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Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids with and without Alcohol

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BACKGROUND: Increased medical and legal cannabis intake is accompanied by greater use of cannabis vaporization and more cases of driving under the influence of cannabis. Although simultaneous Δ^9-tetrahydrocannabinol (THC) and alcohol use is frequent, potential pharmacokinetic interactions are poorly understood. Here we studied blood and plasma vaporized cannabinoid disposition, with and without simultaneous oral low-dose alcohol.

METHODS: Thirty-two adult cannabis smokers (≥1 time/3 months, ≤3 days/week) drank placebo or low-dose alcohol (target approximately 0.065% peak breath-alcohol concentration) 10 min before inhaling 500 mg placebo, low-dose (2.9%) THC, or high-dose (6.7%) THC vaporized cannabis (6 within-individual alcohol-cannabis combinations). Blood and plasma were obtained before and up to 8.3 h after ingestion.

RESULTS: Nineteen participants completed all sessions. Median (range) maximum blood concentrations (C_{max}) for low and high THC doses (no alcohol) were 32.7 (11.4–66.2) and 42.2 (15.2–137) μg/L THC, respectively, and 2.8 (0–9.1) and 5.0 (0–14.2) μg/L 11-OH-THC. With alcohol, low and high dose C_{max} values were 35.3 (13.0–71.4) and 67.5 (18.1–210) μg/L THC and 3.7 (1.4–6.0) and 6.0 (0–23.3) μg/L 11-OH-THC, significantly higher than without alcohol. With a THC detection cutoff of ≥1 μg/L, ≥16.7% of participants remained positive 8.3 h postdose, whereas ≤21.1% were positive by 2.3 h with a cutoff of ≥5 μg/L.

CONCLUSIONS: Vaporization is an effective THC delivery route. The significantly higher blood THC and 11-OH-THC C_{max} values with alcohol possibly explain increased performance impairment observed from cannabis-alcohol combinations. Chosen driving-related THC cutoffs should be considered carefully to best reflect performance impairment windows. Our results will help facilitate forensic interpretation and inform the debate on drugged driving legislation.

Currently, 23 states and the District of Columbia have legalized medical cannabis, and Colorado, Washington, Oregon, and Alaska have decriminalized recreational cannabis intake *(1)*. Per se cannabinoid blood cutoffs for driving under the influence (DUI)[7] include zero tolerance or 1, 2, or 5 μg/L Δ^9-tetrahydrocannabinol (THC) *(2)*; the District of Columbia enacted a 5 μg/L per se law, and Colorado, a 5 μg/L "permissible inference" law. These legal changes have resulted in increased DUI cannabis cases *(3–4)* and more complicated enforcement of cannabinoid drugged driving laws *(5–7)*. A major confounding factor is extended cannabinoid excretion with chronic frequent intake *(6)*. Cannabis plus alcohol, among the most frequent drug combinations identified in driving cases worldwide, shows evidence of increased performance impairment *(5)*. Despite frequent concomitant THC and alcohol intake, little is known about a potential pharmacokinetic interaction. Thus, understanding cannabinoid blood disposition, with and without simultaneous alcohol, is critical for proper test interpretation *(8)*.

Although smoking is the most common cannabis administration route *(9)*, the use of vaporization is increasing rapidly; it provides similar effects *(10–11)* while reducing exposure to harmful pyrolytic byproducts *(12)*

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[7] Nonstandard abbreviations: DUI, driving under the influence; THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol; CBN, cannabinol; NIDA, National Institute on Drug Abuse; 11-OH-THC, 11-hydroxy-THC; THCCOOH, 11-nor-9-carboxy-THC; C_{max}, maximum concentration; t_{max}, time to maximum concentration; AUC, area under the curve; t_{last}, time of last observed concentration; C_{last}, last observed concentration; LOQ, limit of quantification.

and decreasing adverse respiratory symptoms *(13)*. THC is highly lipophilic, rapidly distributing to highly perfused tissues, and later to fat *(14)*. Blood and plasma smoked cannabinoid disposition was recently evaluated in occasional and frequent cannabis smokers *(15–16)*, but vaporized cannabis disposition is not yet fully characterized. The few prior clinical studies had short (≤6 h) time courses and limited metabolite analyses *(10–11)*. As medical cannabis use increases, data on plasma cannabinoids after vaporized cannabis are needed for therapeutic optimization, and blood cannabinoid data are needed for forensic DUI cannabis cases *(17)*.

In this study, we simultaneously evaluated phase I and II cannabinoid disposition in blood and plasma after controlled vaporized cannabis administration, with and without low-dose oral alcohol administration. We hypothesized that cannabinoid delivery and disposition would be similar to that observed with smoking, and that alcohol would not substantially impact cannabinoid pharmacokinetics.

Methods

PARTICIPANTS

Healthy adults provided written informed consent for this University of Iowa Institutional Review Board–approved study. Inclusion criteria were ages 21–55 years; self-reported mean cannabis consumption ≥1 time/3 months but ≤3 days/week over the past 3 months (Cannabis Use Disorders Identification Test *(18)*); self-reported "light" or "moderate" alcohol consumption according to a quantity-frequency-variability scale *(19)*; or if "heavy," not more than 3–4 servings in a typical drinking occasion. Exclusion criteria included past or current clinically significant medical illness; history of clinically significant adverse event associated with cannabis/alcohol intoxication; ≥450 mL blood donation in the 2 weeks preceding drug administration; pregnant/nursing; interest in drug abuse treatment within the past 60 days; and currently taking drugs contraindicated with cannabis or alcohol (ethanol) or known to affect driving.

STUDY DESIGN

Participants entered the clinical research unit 10–16 h before drug administration to preclude intoxication at dosing. Over 10 min, participants drank ad libitum placebo (−) (apple, orange, or cranberry juice, consistent within individuals, with ethanol-swabbed rim and topped with 1 mL ethanol to mimic alcohol taste and odor) or low-dose (+) 90% grain ethanol (to produce approximately 0.065% peak breath alcohol concentration) mixed with juice. After drinking, they orally inhaled 500 mg placebo (P) [mean 0.008% (SD 0.002%) THC/mean 0.001% (SD 0.001%) cannabidiol (CBD)/mean 0.009% (SD 0.003%) cannabinol (CBN)], low-THC (L) [mean 2.9% (SD 0.14%) THC/mean 0.05% (SD 0.00%) CBD/mean 0.22% (SD 0.02%) CBN], or high-THC (H) [mean 6.7% (SD 0.05%) THC/mean 0.19% (SD 0.01%) CBD/mean 0.37% (SD 0.03%) CBN] vaporized ground bulk cannabis [210 °C, standard (approximately 8 L) balloon volume, Volcano® Medic, Storz & Bickel] ad libitum over 10 min (see Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue6). We obtained bulk cannabis through the National Institute on Drug Abuse (NIDA) Chemistry and Physiological Systems Research Branch. In this within-individual design, participants received all 6 alcohol/cannabis doses, in randomized order, in sessions separated by ≥1 week to prevent cannabinoid carryover from study interventions. Blood was collected via indwelling peripheral venous catheter into gray-top potassium oxalate/sodium fluoride Vacutainer® tubes (VWR Scientific) at baseline (−0.8 h) and 0.17, 0.42, 1.4, 2.3, 3.3, 4.8, 6.3, and 8.3 h after start of inhalation, stored on ice ≤2 h, with a second sample centrifuged at 1600*g* for 10 min. Blood and plasma were transferred into 3.6-mL Nunc® cryotubes (Thomas Scientific), stored at −20 °C, and analyzed within 3 months, on the basis of our previous stability study *(20)*.

BLOOD AND PLASMA ANALYSIS

We quantified blood and plasma cannabinoids by a previously published LC-MS/MS method *(21)*. Briefly, 0.5 mL blood or plasma was protein-precipitated with ice-cold acetonitrile, and supernatants were diluted and solid-phase extracted with Bond-Elut Plexa cartridges (Agilent Technologies). Linear ranges were 1–100 μg/L for THC, 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), CBD, and CBN; 5–250 μg/L for THCCOOH-glucuronide; and 0.5–50 μg/L for THC-glucuronide. Interassay (n = 30) analytical accuracy and imprecision were 93.1%–109.3% and 4.5%–12.8%, respectively.

DATA ANALYSIS

We performed noncompartmental analyses with Phoenix WinNonLin® 6.3 for Windows (Pharsight). Maximum concentration (C_{max}), C_{max} accounting for baseline ($C_{max\text{-}BL}$), time to maximum concentration (t_{max}), area under the curve (AUC) from 0 to 8.3 h postdose ($AUC_{0-8.3h}$), $AUC_{0-8.3h}$ accounting for baseline ($AUC_{>BL-8.3h}$), time of last observed concentration (t_{last}), and last observed concentration (C_{last}) were compared with SPSS® Statistics version 19 for Windows (IBM). For statistical purposes, concentrations less than the limit of quantification (LOQ) were set to 0. We compared overall alcohol and cannabis effects on pharmacokinetic parameters for each analyte with factorial repeated-measures ANOVA (factors: cannabis, alcohol, cannabis*alcohol) with Bonfer-

roni correction for individuals who completed all 6 sessions. When the Mauchly sphericity test was violated, the Greenhouse–Geisser correction was used. Friedman's ANOVA with pairwise post hoc comparisons was used to determine within-individual dose differences, overall and by time point. For time point analyses, we used the conservative Bonferroni correction for multiple comparisons ($P < 0.05/9$ measurements $= P < 0.006$). Blood/plasma or metabolite ratios were calculated when quantifiable (positive) data were available. We assessed THCCOOH-glucuronide/THCCOOH ratios with factorial repeated-measures ANOVA in SPSS, with factors alcohol and cannabis, and covariate time.

Results

PARTICIPANTS

Thirty-two healthy adults (22 men, ages 21–42 years, 72% white) participated in the study (Table 1). Most participants consumed cannabis ≥2 times/month and reported intake within a week before admission. Two individuals (participants 17 and 20) self-reported last intake 4 and 6 months ago, respectively, despite reporting overall mean consumption at ≥1 time/3 months. Nineteen participants completed all 6 sessions (P−/+, L−/+, H−/+); there were no significant differences in cannabis history, age, or body mass index between these and the 13 noncompleters [Mann–Whitney *U* (exact) test]. One participant *(24)* withdrew due to nausea/emesis from cannabis administration; other noncompleters withdrew for personal reasons.

BLOOD AND PLASMA CANNABINOIDS

In total, 1324 blood and 1327 plasma samples were quantified for cannabinoids. Blood and plasma pharmacokinetic parameters for 19 completers are presented in Tables 2–4 and online Supplemental Tables 2–4. Blood C_{max}, with and without accounting for baseline concentrations for THC, 11-OH-THC, and CBN, were significantly higher when alcohol was coadministered with cannabis; in addition, blood THCCOOH-glucuronide t_{max} was earlier and blood CBN $AUC_{0-8.3h}$ was higher with concomitant alcohol (Table 3 and online Supplemental Table 3). In plasma, alcohol significantly increased THC, 11-OH-THC, and CBN C_{max} and CBD $C_{max\text{-}BL}$ (Table 4 and online Supplemental Table 4). Significant additional alcohol-cannabis interactions were observed for 11-OH-THC (C_{max}, C_{last}, t_{last} in blood; C_{last} in plasma) and plasma CBD (C_{max}). Blood and plasma THC $AUC_{0-8.3h}$ L and H doses were significantly higher than placebo ($P < 0.001$ and $P = 0.036$ respectively, in both blood and plasma). Accounting for baseline revealed a significant overall cannabis effect on $AUC_{>BL-8.3h}$ and significantly higher $AUC_{>BL-8.3h}$ after H vs L cannabis. Significant overall cannabinoid concentration differences ($P < 0.006$) were observed in blood through 3.3 h (Fig. 1 and online Supplemental Fig. 1) for THC and 11-OH-THC, throughout the time course for THCCOOH, and beginning at 1.4 h for THCCOOH-glucuronide. Only H− and H+ showed significant THCCOOH-glucuronide differences (post hoc analysis) relative to P− and P+. Plasma observations were similar to blood (Fig. 1 and online Supplemental Fig. 2). Fig. 1 and online Supplemental Figs. 2 and 3 present post hoc within-individual dose differences at individual collection times. No significant blood or plasma L vs H cannabinoid differences were observed at any discrete time point for any analyte except plasma CBD immediately postinhalation (Fig. 1). Median THC-glucuronide, CBD, and CBN t_{last} occurred within 0.5 h after inhalation. For all dosing conditions, ≥10.5% completers had blood THC ≥1 μg/L at baseline and ≥16.7% throughout 8.3 h postdose, even after placebo cannabis (Fig. 2). With a 2 μg/L blood THC cutoff, 5.3%–10.5% were positive at baseline for all doses, and only 1 participant was positive after 0.42 h for P−. By 3.3 h, <50% were positive after any dose (Fig. 2). In this cohort of occasional to moderate smokers, 0%–5.9% completers had blood THC ≥5 μg/L at baseline (all conditions), with ≤21.1% THC ≥5 μg/L by 2.3 h. Thus, 78.9% of occasional to moderate cannabis smokers were negative after only 2.3 h with a THC ≥5 μg/L cutoff.

Pharmacokinetic parameters for all participants are presented in online Supplemental Tables 5–11. There were no significant differences [$P > 0.44$, Mann–Whitney *U* (exact) test] between completers and noncompleters in cannabis smoking history, age, weight, or body mass index. High interindividual variability was observed in THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide concentrations. Observed THC, 11-OH-THC, CBD, and CBN t_{max} occurred immediately postinhalation, whereas THCCOOH, THC-glucuronide, and THCCOOH-glucuronide t_{max} values reflected additional time needed for further metabolism. After active doses, full-study population median THC and 11-OH-THC observed t_{last} occurred at 3.5–6.4 and 1.4–3.3 h, respectively. Median THCCOOH and THCCOOH-glucuronide t_{last} values extended ≥8.3 h. CBD and CBN t_{last} occurred within 0.5 h.

On the basis of pharmacokinetic data, Participant 25 may have accessed active cannabis during his P+ session, despite being under observation throughout his stay (see online Supplemental Fig. 3). Blood and plasma THC C_{max} were 18.5 and 25.6 μg/L. This participant's oral fluid indicated he was negative on admission the night before dosing but positive just before dosing. It is possible these high concentrations resulted from dosing error; however, there was no indication from careful record review that an error occurred. These data were excluded from pharmacokinetic data analysis.

Table 1. Self-reported demographic characteristics and recent cannabis and alcohol consumption history of 32 healthy occasional cannabis smokers.

Participant	Sex	Age, years	Race/ethnicity	BMI, kg/m^2	Alcohol frequency	Typical drinks per occasion	Cannabis frequency	Hours "stoned" on typical cannabis occasion[a]	Time since last cannabis consumed, days	Amount last consumed, joint or joint equivalent[b]	Doses received, n (reason for withdrawal)
1	F	30.6	W[c]	21.4	2–4×/m	2–4	2–3×/wk	1–2	1	2	2 (P)
2	M	23.7	W	24.3	2–3×/wk	2–4	2–4×/m	1–2	1	1	6
3	F	28.4	AA	23.8	≥4×/wk	2–4	2–4×/m	3–4	14	1	6
4	M	27.8	W	33.2	2–3×/wk	2–4	2–3×/wk	1–2	1	1	3 (P)
5	M	21.9	W	24.7	2–3×/wk	5–6	2–4×/m	1–2	6	1	6
6	M	37.8	W	26.1	2–3×/wk	2–4	2–3×/wk	1–2	3	2.5	6
7	M	26.6	W	21.6	≤1×/m	2–4	≤1×/m	1–2	11	3.5	6
8	F	26.3	W	20.0	2–3×/wk	2–4	2–3×/wk	3–4	1	0.25	6
9	M	25.8	W	40.6	2–4×/m	2–4	2–3×/wk	1–2	0.3	0.5	6
10	M	26.1	H	31.5	2–4×/m	1–2	2–3×/wk	1–2	3	1	6
11	M	26.9	W	22.9	2–3×/wk	1–2	≤1×/m	3–4	2	1	3 (P)
12	M	23.2	W	19.5	2–3×/wk	2–4	2–3×/wk	3–4	2	1	6
13	M	23.1	W	23.9	2–4×/m	2–4	≤1×/m	1–2	2	0.25	6
14	M	21.1	W	20.6	2–3×/wk	5–6	2–3×/wk	1–2	2	2	3 (P)
15	M	32.3	O, H	28.9	2–3×/wk	2–4	2–3×/wk	1–2	4	1	6
16	F	23.4	W	23.3	2–3×/wk	2–4	2–4×/m	3–4	4	1	6
17	F	30.3	AA	24.1	2–3×/wk	2–4	≤1×/m	<1	120	1	6
18	M	24.6	W	23.3	2–3×/wk	2–4	2–4×/m	1–2	7	0.8	6
19	M	40.8	W	31.7	2–3×/wk	2–4	2–4×/m	3–4	5	3	2 (P)
20	F	21.8	W	30.8	2–4×/m	2–4	2–3×/wk	1–2	183	0.5	4 (P)
21	M	42.1	W	24.2	2–4×/m	1–2	≤1×/m	1–2	45	2	2 (P)
22	M	39.4	W, As	34.6	2–4×/m	2–4	2–4×/m	3–4	1	4.5	4 (P)
23	M	21.1	AI, As, AA, W	24.0	2–4×/m	2–4	2–3×/wk	5–6	2	1	2 (P)
24	F	24.6	W, H	19.1	2–3×/wk	2–4	2–4×/m	3–4	28	0.5	3 (AE)
25[d]	M	21.8	W	32.7	≤1×/m	1–2	2–4×/m	1–2	7	0.13	6
26	M	29.0	O	28.0	2–3×/wk	2–4	≤1×/m	<1	30	0.2	2 (P)
27	F	23.0	W	21.0	2–3×/wk	2–4	2–4×/m	5–6	7	0.3	2 (P)
28	F	21.7	AA, W	23.0	2–4×/m	1–2	2–3×/wk	1–2	1.1	1.5	6
29	M	28.7	W	18.3	2–3×/wk	2–4	≤1×/m	3–4	45	0.5	6
30	M	28.1	W	48.3	2–4×/m	2–4	2–4×/m	3–4	5	1	6
31	F	22.9	W	21.6	2–4×/m	5–6	2–3×/wk	3–4	1	1	6
32	M	22.7	W	26.1	2–4×/m	1–2	2–4×/m	1–2	8	1	3 (P)
Completers											
Median		25.8		23.9					4.0	1.0	
Mean		26.1		26.3					12.5	1.0	
SD		4.1		7.5					27.9	0.8	
All											
Median		26.0		24.0					4.0	1.0	
Mean		27.1		26.2					17.3	1.2	
SD		5.8		6.6					38.0	1.0	

[a] Wording originates from Cannabis Use Disorders Identification Test, source of self-reported cannabis frequency data.
[b] Cannabis amount last consumed is based on empirically normalized joint consumption, to account for various administration routes and self-reported sharing between multiple individuals.
[c] W, white; AA, African American; H, Hispanic or Latino; As, Asian; O, other; AI, American Indian/Native American; P, withdrew for personal reasons (job obligations/scheduling/choice); AE, withdrew due to adverse event (nausea/emesis or dizziness, related to study drugs or other study procedures).
[d] May have consumed active cannabis during placebo-alcohol session.

Table 2. Blood and plasma pharmacokinetic parameters after controlled vaporized cannabis administration with and without oral alcohol.[a]

	Blood		Plasma	
Analyte and parameter	No alcohol	Alcohol	No alcohol	Alcohol
THC (LOQ 1 μg/L)				
C_{max}, μg/L				
Placebo	2.1 (0–7.6)[b,c]	0.6 (0–5.2)[b,c]	3.2 (0–9.8)[b,c]	1.4 (0–9.6)[b,c]
Low	32.7 (11.4–66.2)[b,c]	35.3 (13.0–71.4)[b,c]	46.5 (16.6–114)[b,c]	48.6 (21.7–102)[b,c]
High	42.2 (15.2–137)[b,c]	67.5 (18.1–210)[b,c]	62.1 (23.6–196)[b,c]	97.8 (24.5–339)[b,c]
$C_{max\text{-}BL}$, μg/L				
Placebo	1.7 (0–5.3)[b,c]	0 (0–3.2)[b,c]	2.4 (0–9.2)[b,c]	0.7 (–0.7–9.6)[b,c]
Low	32.7 (11.4–66.2)[b,c]	35.3 (8.1–71.4)[b,c]	45.7 (16.6–113)[b,c]	48.6 (2.3–102)[b,c]
High	42.2 (15.2–137)[b,c]	67.5 (18.1–204)[b,c]	62.1 (23.6–196)[b,c]	96.1 (24.5–332)[b,c]
t_{max}, h				
Placebo	0.17 (0.15–6.3)	0.18 (0.07–≥8.3)	0.17 (0.15–6.3)	0.22 (0.07–≥8.3)
Low	0.17 (0.15–0.33)	0.17 (0.15–0.25)	0.17 (0.15–0.33)	0.17 (0.15–0.25)
High	0.17 (0.15–0.3)	0.17 (0.12–0.37)	0.17 (0.15–0.30)	0.17 (0.12–0.37)
$AUC_{0\text{–}8.3h}$, h · μg/L				
Placebo	1.1 (0–53.2)[d]	0.3 (0–36.4)[d]	3.4 (0–66.6)[d]	1.3 (0–103623)[d]
Low	31.9 (10.6–84.2)[d]	36.2 (18.0–52.2)[d]	44.6 (14.1–124)[d]	49.4 (26.9–80)[d]
High	43.1 (10.6–113)[d]	62.2 (13.2–1445)[d]	56.2 (15.9–182)[d]	93.2 (19.4–2370)[d]
$AUC_{>BL\text{–}8.3h}$, h · μg/L				
Placebo	0.6 (0–7.0)[b]	0 (0–19.6)[b]	1.4 (0–7.7)[b]	0.3 (0–7.4)[b]
Low	21.7 (6.9–38.4)[b]	18.7 (7.6–33.4)[b]	29.2 (9.3–56.5)[b]	24.9 (14.1–49.3)[b]
High	29.4 (6.8–77.9)[b]	33.7 (8.8–83.5)[b]	43.4 (9.7–124)[b]	51.6 (14.1–132)[b]
t_{last}, h				
Placebo	0.42 (0.15–≥8.3)[b]	4.8 (0.17–≥8.3)[b]	0.4 (0.15–≥8.3)[b]	4.3 (0.17–≥8.3)[b]
Low	3.5 (0.70–≥8.3)[b]	3.5 (1.3–≥8.3)[b]	4.8 (0.70–≥8.3)[b]	6.3 (1.3–≥8.3)[b]
High	4.8 (0.82–≥8.3)[b]	3.7 (1.4–≥8.3)[b]	6.3 (1.3–≥8.3)[b]	6.4 (1.4–≥8.3)[b]
11-OH-THC (LOQ 1 μg/L)				
C_{max}, μg/L				
Placebo	0 (0–2.5)[b,c,e]	0 (0–2.4)[b,c,e]	0 (0–4.3)[b,c]	0 (0–3.2)[b,c]
Low	2.8 (0–9.1)[b,c,e]	3.7 (1.4–6.0)[b,c,e]	4.1 (0–13.7)[b,c]	4.8 (1.3–8.0)[b,c]
High	5.0 (0–14.2)[b,c,e]	6.0 (0–24.8)[b,c,e]	7.0 (1.0–20.3)[b,c]	7.5 (0–27.3)[b,c]
$C_{max\text{-}BL}$, μg/L				
Placebo	0 (0–1.1)[b,c,e]	0 (0–1.4)[b,c,e]	0 (0–1.1)[b]	0 (0–1.8)[b]
Low	2.8 (0–9.1)[b,c,e]	3.3 (1.4–6.0)[b,c,e]	3.7 (0–13.7)[b]	4.4 (1.3–8.0)[b]
High	5.0 (0–12.8)[b,c,e]	6.0 (0–23.3)[b,c,e]	7.0 (1.0–20.3)[b]	7.5 (0–25.4)[b]
t_{max}, h				
Placebo	3.2 (0.17–6.3)	0.18 (0.17–2.3)	1.8 (0.15–4.8)	0.18 (0.17–4.8)
Low	0.19 (0.15–0.58)	0.17 (0.15–0.42)	0.17 (0.15–0.4)	0.22 (0.15–0.48)
High	0.18 (0.15–0.43)	0.18 (0.12–0.42)	0.18 (0.15–0.4)	0.18 (0.12–0.53)
$AUC_{0\text{–}8.3h}$, h · μg/L				
Placebo	0 (0–18.2)[b]	0 (0–11.6)[b]	0 (0–28.3)[b]	0 (0–21.2)[b]
Low	3.4 (0–25.9)[b]	4.4 (1.1–15.0)[b]	5.8 (0–39.0)[b]	6.4 (1.1–28.3)[b]
High	6.8 (0–29.8)[b]	7.2 (0–42.0)[b]	9.8 (0.4–48.3)[b]	11.8 (0–51.3)[b]

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Table 2. Blood and plasma pharmacokinetic parameters after controlled vaporized cannabis administration with and without oral alcohol.[a] *(Continued from page 854)*

	Blood		Plasma	
Analyte and parameter	No alcohol	Alcohol	No alcohol	Alcohol
$AUC_{>BL–8.3h}$, h · μg/L				
Placebo	0 (0–0.5)[b]	0 (0–4.3)[b]	0 (0–2.4)[b]	0 (0–0.5)[b]
Low	3.2 (0–8.1)[b]	4.0 (1.1–12.2)[b]	5.5 (0–12.3)[b]	6.3 (1.2–12.6)[b]
High	6.8 (0–28.8)[b]	7.2 (0–29.4)[b]	9.8 (0.42–41.5)[b]	11.8 (0–33.4)[b]
t_{last}, h				
Placebo	(2.3–≥8.3) (*n* = 2)	6.3 (0.42–≥8.3) (n=4)	4.8 (0.15–≥8.3) (n=4)	3.4 (0.17–≥8.3) (n=6)
Low	1.4 (0.20–≥8.3)[c,e]	1.5 (0.42–≥8.3)[c,e]	2.3 (0.40–≥8.3)	2.3 (0.42–≥8.3)
High	3.0 (0.42–≥8.3)[c,e]	2.3 (0.42–≥8.3)[c,e]	3.3 (0.18–≥8.3)	3.3 (0.42–≥8.3)
THCCOOH (LOQ 1 μg/L)				
C_{max}, μg/L				
Placebo	2.9 (0–67.0)[b]	2.9 (0–62.8)[b]	5.0 (0–107)[b]	3.8 (0–97.5)[b]
Low	14.5 (4.4–84.2)[b]	15 (5.4–75.0)[b]	25.3 (6.2–137)[b]	21.1 (7.2–133)[b]
High	23.8 (2.6–66.6)[b]	17.4 (3.4–95.4)[b]	38.1 (2.9–116)[b]	25.2 (5.1–134)[b]
C_{max-BL}, μg/L				
Placebo	0.5 (–0.3–2.3)[b]	0.4 (–1.1–43.3)[b]	1.0 (–1.3–3.8)[b]	0 (–20.2–41.4)[b]
Low	10.0 (4.4–22.2)[b]	9.4 (0–21.2)[b]	17.5 (6.2–32.4)[b]	13.7 (–0.8–47.3)[b]
High	17.5 (2.6–36.9)[b]	11.9 (0–53.2)[b]	26.0 (2.9–61.1)[b]	18.8 (–10.6–82.9)[b]
t_{max}, h				
Placebo	0.42 (0.15–3.3)	0.32 (0.17–≥8.3)	0.40 (0.15–3.3)	0.40 (0.07–3.4)
Low	0.40 (0.17–1.6)	0.40 (0.22–3.5)	0.40 (0.17–1.3)	0.40 (0.15–3.5)
High	0.40 (0.17–0.82)	0.42 (0.15–3.3)	0.40 (0.17–1.3)	0.42 (0.15–3.3)
$AUC_{0–8.3h}$, h · μg/L				
Placebo	17.1 (0–437)[b]	13.5 (0–358)[b]	25.2 (0–682)[b]	20.7 (0–568)[b]
Low	56.8 (13.4–579)[b]	56.8 (11.8–424)[b]	97.3 (18.2–883)[b]	84.2 (24.8–659)[b]
High	88.4 (9.6–361)[b]	62.5 (8.3–572)[b]	134 (14.9–665)[b]	100 (16.6–816)[b]
$AUC_{>BL–8.3h}$, h · μg/L				
Placebo	0.4 (0–3.7)[b]	0.1 (0–279)[b]	1.1 (0–10.6)[b]	0 (0–137)[b]
Low	27.7 (9.6–70.8)[b]	26.2 (0–85.9)[b]	40.8 (18.2–83.0)[b]	46.4 (0–181)[b]
High	51.7 (9.6–121)[b]	41.8 (0–262)[b]	69.8 (14.9–235)[b]	58.8 (0–396)[b]
t_{last}, h				
Placebo	≥8.3 (0.18–≥8.3)	≥8.3 (0.18–≥8.3)	≥8.3 (0.43–≥8.3)	≥8.3 (1.4–≥8.3)
Low	≥8.3 (8.2–≥8.3)	≥8.3 (4.3–≥8.3)	≥8.3 (≥8.3–≥8.3)	≥8.3 (≥8.3–≥8.3)
High	≥8.3 (4.8–≥8.3)	≥8.3 (3.3–≥8.3)	≥8.3 (≥8.3–≥8.3)	≥8.3 (6.2–≥8.3)
THCCOOH-glucuronide (LOQ 5 μg/L)				
C_{max}, μg/L				
Placebo	6.4 (0–156)[b]	6.0 (0–118)[b]	11.1 (0–340)[b]	17.5 (0–155)[b]
Low	25.9 (0–213)[b]	27.5 (5.2–152)[b]	31.3 (6.2–227)[b]	47.6 (6.1–219)[b]
High	48.2 (0–145)[b]	31.6 (6.6–259)[b]	55.2 (9.2–251)[b]	47.4 (7.5–370)[b]
C_{max-BL}, μg/L				
Placebo	0 (–4.7–23)[b]	1.4 (0–74.4)[b]	0.9 (–6.0–93.0)[b]	0.9 (–35.9–53.2)[b]
Low	14.3 (–7.0–31.1)[b]	19.0 (5.2–39.0)[b]	22.5 (–3.9–108)[b]	30.5 (6.0–129)[b]
High	24.0 (0–81.2)[b]	24.5 (6.6–87.0)[b]	33.4 (–4.7–107)[b]	34.0 (–120–200)[b]

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Table 2. Blood and plasma pharmacokinetic parameters after controlled vaporized cannabis administration with and without oral alcohol.[a] *(Continued from page 855)*

	Blood		Plasma	
Analyte and parameter	No alcohol	Alcohol	No alcohol	Alcohol
t_{max}, h				
Placebo	1.9 (0.17–6.3)[c]	1.4 (0.42–6.3)[c]	3.3 (0.15–≥8.3)	1.8 (0.15–6.3)
Low	2.3 (0.17–6.4)[c]	1.7 (1.3–6.3)[c]	1.7 (0.17–≥8.3)	2.4 (0.42–≥8.3)
High	2.3 (1.3–≥8.3)[c]	1.7 (1.3–≥8.3)[c]	3.3 (0.82–≥8.3)	1.7 (0.18–≥8.3)
$AUC_{0–8.3h}$, h · μg/L				
Placebo	30.0 (0–1111)[b]	22.0 (0–817)[b]	55.5 (0–1796)[b]	63.2 (0–855)[b]
Low	173 (0–1595)[b]	177 (24.3–907)[b]	181 (7.9–1425)[b]	301 (21.9–1255)[b]
High	320 (0–990)[b]	237 (28.1–1796)[b]	355 (8.0–1656)[b]	245 (8.1–2656)[b]
$AUC_{>BL–8.3h}$, h · μg/L				
Placebo	0 (0–49.4)[b]	1.8 (0–519)[b]	0.36 (0–129)[b]	1.5 (0–174)[b]
Low	86.1 (0–205)[b]	92.2 (19.9–216)[b]	77.0 (0–451)[b]	115 (18.1–677)[b]
High	114 (0–373)[b]	144 (28.1–384)[b]	126 (0–481)[b]	136 (0–1171)[b]
t_{last}, h				
Placebo	≥8.3 (4.8–≥8.3)[b]	≥8.3 (2.3–≥8.3)[b]	≥8.3 (3.3–≥8.3)	≥8.3 (1.4–≥8.3)
Low	≥8.3 (4.8–≥8.3)[b]	≥8.3 (4.8–≥8.3)[b]	≥8.3 (3.3–≥8.3)	≥8.3 (4.8–≥8.3)
High	≥8.3 (≥8.3–≥8.3)[b]	≥8.3 (4.8–≥8.3)[b]	≥8.3 (0.82–≥8.3)	≥8.3 (1.6–≥8.3)

[a] Data are median (range) from 19 occasional-to-moderate cannabis smokers who participated in all dosing sessions (lower n reflects fewer participants with calculable ANOVA results owing to negative placebo samples). See online Supplemental Table 2 for C_{last} and THC-glucuronide, cannabidiol, and cannabinol data. Statistical analyses by factorial repeated-measures ANOVA. Cannabis was administered with Volcano Medic vaporizer: 500 mg placebo [0.008% (0.002%) THC], low-dose [2.9% (0.14%) THC], or high-dose [6.7% (0.05%) THC] THC. Active alcohol dose was calculated to produce approximate 0.065% peak breath alcohol concentration.

[b] Significant overall cannabis dose effect ($P < 0.05$) by factorial repeated-measures ANOVA (see Tables 3 and 4).

[c] Significant overall alcohol dose effect ($P < 0.05$) by factorial repeated-measures ANOVA (see Tables 3 and 4).

[d] Overall cannabis $P < 0.06$ by factorial repeated-measures ANOVA. Post-hoc analysis revealed significant low and high vs placebo cannabis effect, but no significant low vs high cannabis effect (see Tables 3 and 4).

[e] Significant overall alcohol-cannabis effect ($P < 0.05$) by factorial repeated-measures ANOVA (see Tables 3 and 4).

BLOOD/PLASMA RATIOS

Median (range) blood/plasma ratios were 0.71 (0.13–1.5) THC (n = 684), 0.73 (0.42–1.4) 11-OH-THC (n = 409), 0.65 (0.39–1.5) THCCOOH (n = 1112), 0.55 (0.40–1.3) THC-glucuronide (n = 12), 0.80 (0.13–7.9) THCCOOH-glucuronide (n = 926), 0.73 (0.48–1.0) CBD (n = 31), and 0.86 (0.49–1.3) CBN (n = 71). THC and metabolite blood/plasma ratios did not vary by time or dose (see online Supplemental Fig. 4).

THCCOOH-GLUCURONIDE/THCCOOH RATIOS

Blood and plasma THCCOOH-glucuronide/THCCOOH ratios decreased immediately (within the first half-hour postdose) after inhaling active cannabis and subsequently rose, with substantial interindividual variability (see online Supplemental Fig. 5). Alcohol, cannabis, and cannabis*time all significantly affected THCCOOH-glucuronide/THCCOOH in blood [$F(1,72) = 8.173$, $P = 0.006$; $F(1.71,123.06) = 24.17$, $P < 0.001$; and $F(1.71,123.06) = 15.12$, $P < 0.001$, respectively] and plasma [$F(1,69) = 10.51$, $P = 0.002$; $F(2,138) = 8.01$, $P = 0.001$; and $F(2,138) = 5.542$, $P = 0.005$]. Active alcohol conditions (+) produced higher THCCOOH-glucuronide/THCCOOH ratios than placebo alcohol (−).

Discussion

Here we obtained complete data for blood and plasma phase I and II cannabinoid concentrations following vaporized cannabis, with and without low-dose alcohol. Inhaling vaporized bulk cannabis produced blood and plasma cannabinoid concentrations and pharmacokinetic curves similar to those of smoking *(11, 15–16)*. Desrosiers et al. *(16)* recently observed 34.4 (16.5–49.5) μg/L blood THC C_{max} in 14 frequent smokers (≥4 times/week) 0.5 h after smoking one 6.8% THC cigarette, similar to our occasional smokers' L dose (500 mg, 2.9% THC) at t_{max} 0.17 h [32.7 (11.4–66.2) μg/L THC]. However, inhaled THC concentrations peak before the last puff, rapidly decreasing as lipophilic THC is distributed to the tissues and rapidly metabolized *(14)*.

Table 3. Effects of alcohol, cannabis, and alcohol*cannabis combination on blood cannabinoid pharmacokinetic parameters.[a]

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
THC							
C_{max}							
Alcohol		19	8.03	1	18	0.56	**0.011**
Cannabis			42.84	1.21	21.73		**<0.001**[b]
	Low vs placebo		139.71	1	18	0.94	**<0.001**
	High vs placebo		57.23	1	18	0.87	**<0.001**
	Low vs high		12.14	1	18	0.63	**0.003**
Alcohol*cannabis			1.91	1.15	20.74		0.182[b]
$C_{max\text{-}BL}$							
Alcohol		18	8.03	1	17	0.57	**0.011**
Cannabis			42.00	1.21	20.62		**<0.001**[b]
	Low vs placebo		123.28	1	17	0.94	**<0.001**
	High vs placebo		55.74	1	17	0.88	**<0.001**
	Low vs high		13.25	1	17	0.66	**0.002**
Alcohol*cannabis			3.20	1.17	19.97		0.084[b]
t_{max}							
Alcohol		8	0.53	1	7	0.27	0.490
Cannabis			2.73	1.00	7.01		0.142[b]
	Low vs placebo		2.79	1	7	0.53	0.139
	High vs placebo		2.68	1	7	0.53	0.146
	Low vs high		0.20	1	7	0.16	0.672
Alcohol*cannabis			0.49	1.00	7.02		0.509[b]
t_{last}							
Alcohol		8	1.46	1	7	0.42	0.266
Cannabis			9.18	1.15	8.04		**0.014**[b]
	Low vs placebo		10.11	1	7	0.77	**0.016**
	High vs placebo		9.34	1	7	0.76	**0.018**
	Low vs high		0.61	1	7	0.28	0.461
Alcohol*cannabis			1.30	1.07	7.52		0.295[b]
$AUC_{0\text{-}8.3h}$							
Alcohol		19	1.35	1	18	0.26	0.261
Cannabis			4.09	1.00	18.05		0.058[b]
	Low vs placebo		245.38	1	18	0.97	**<0.001**
	High vs placebo		5.13	1	18	0.47	**0.036**
	Low vs high		2.53	1	18	0.35	0.129
Alcohol*cannabis			1.26	1.00	18.04		0.277[b]
$AUC_{>BL\text{-}8.3h}$							
Alcohol		18	0.50	1	17	0.17	0.488
Cannabis			47.43	1.21	20.60		**<0.001**[b]
	Low vs placebo		119.56	1	17	0.94	**<0.001**
	High vs placebo		59.62	1	17	0.88	**<0.001**
	Low vs high		17.18	1	17	0.71	**0.001**
Alcohol*cannabis			0.63	1.27	21.55		0.473[b]

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Table 3. Effects of alcohol, cannabis, and alcohol*cannabis combination on blood cannabinoid pharmacokinetic parameters.[a]
(Continued from page 857)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
11-OH-THC							
C_{max}							
Alcohol		19	9.95	1	18	0.60	**0.005**
Cannabis			28.88	1.16	20.81		**<0.001**[b]
	Low vs placebo		98.45	1	18	0.92	**<0.001**
	High vs placebo		38.44	1	18	0.83	**<0.001**
	Low vs high		10.47	1	18	0.61	**0.005**
Alcohol*cannabis			4.49	1.23	22.19		**0.039**[b]
	Low vs placebo		0.52	1	18	0.17	0.481
	High vs placebo		5.89	1	18	0.50	**0.026**
	Low vs high		3.87	1	18	0.42	0.065
$C_{max\text{-}BL}$							
Alcohol		18	8.50	1	17	0.58	**0.010**
Cannabis			29.61	1.16	19.74		**<0.001**[b]
	Low vs placebo		87.23	1	17	0.91	**<0.001**
	High vs placebo		39.09	1	17	0.83	**<0.001**
	Low vs high		12.00	1	17	0.64	**0.003**
Alcohol*cannabis			4.93	1.27	21.51		**0.030**[b]
	Low vs placebo		0.62	1	17	0.19	0.444
	High vs placebo		6.51	1	17	0.53	**0.021**
	Low vs high		4.26	1	17	0.45	0.055
t_{max}							
Alcohol	Low vs high[c]	16	1.63	1	15	0.31	0.221
Cannabis	Low vs high[c]		0.09	1	15	0.08	0.769
Alcohol*cannabis	Low vs high[c]		2.30	1	15	0.36	0.150
t_{last}							
Alcohol	Low vs high[c]	16	0.01	1	15	0.03	0.910
Cannabis	Low vs high[c]		16.35	1	15	0.72	**0.001**
Alcohol*cannabis	Low vs high[c]		4.81	1	15	0.50	**0.043**
$AUC_{0\text{–}8.3h}$							
Alcohol		18	0.75	1	17	0.21	0.398
Cannabis			25.15	1.10	18.62		**<0.001**[b]
	Low vs placebo		53.57	1	17	0.87	**<0.001**
	High vs placebo		28.25	1	17	0.79	**<0.001**
	Low vs high		14.08	1	17	0.67	**0.002**
Alcohol*cannabis			0.60	1.20	20.37		0.475[b]
$AUC_{>BL\text{–}8.3h}$							
Alcohol		18	0.92	1	17	0.23	0.351
Cannabis			24.39	1.10	18.77		**<0.001**[b]
	Low vs placebo		63.20	1	17	0.89	**<0.001**
	High vs placebo		29.62	1	17	0.80	**<0.001**
	Low vs high		13.60	1	17	0.67	**0.002**
Alcohol*cannabis			0.10	1.29	21.99		0.823[b]

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Table 3. Effects of alcohol, cannabis, and alcohol*cannabis combination on blood cannabinoid pharmacokinetic parameters.[a]
(Continued from page 858)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
THCCOOH							
C_{max}							
Alcohol		19	0.03	1	18	0.04	0.871
Cannabis			27.35	1.39	25.02		**<0.001**[b]
	Low vs placebo		48.59	1	18	0.85	**<0.001**
	High vs placebo		46.38	1	18	0.85	**<0.001**
	Low vs high		6.94	1	18	0.53	**0.017**
Alcohol*cannabis			0.03	1.30	23.32		0.922[b]
$C_{max\text{-}BL}$							
Alcohol		18	0.00	1	17	0.00	0.995
Cannabis			26.34	1.44	24.43		**<0.001**[b]
	Low vs placebo		21.34	1	17	0.75	**<0.001**
	High vs placebo		32.78	1	17	0.81	**<0.001**
	Low vs high		17.30	1	17	0.71	**0.001**
Alcohol*cannabis			1.56	2	34		0.225
t_{max}							
Alcohol		13	0.56	1	12	0.21	0.470
Cannabis			1.46	1.03	12.40		0.250[b]
	Low vs placebo		1.33	1	12	0.32	0.271
	High vs placebo		1.61	1	12	0.34	0.229
	Low vs high		0.82	1	12	0.25	0.383
Alcohol*cannabis			0.05	1.05	12.64		0.842[b]
t_{last}							
Alcohol		13	0.25	1	12	0.14	0.628
Cannabis			4.10	1.04	12.43		0.064[b]
	Low vs placebo		4.50	1	12	0.52	0.055
	High vs placebo		3.81	1	12	0.49	0.075
	Low vs high		0.60	1	12	0.22	0.455
Alcohol*cannabis			0.08	1.03	12.34		0.784[b]
$AUC_{0\text{–}8.3h}$							
Alcohol		19	0.18	1	18	0.10	0.675
Cannabis			17.94	1.49	26.87		**<0.001**[b]
	Low vs placebo		26.06	1	18	0.77	**<0.001**
	High vs placebo		36.45	1	18	0.82	**<0.001**
	Low vs high		3.43	1	18	0.40	0.080
Alcohol*cannabis			0.34	1.21	21.83		0.607[b]
$AUC_{>BL\text{–}8.3h}$							
Alcohol		18	0.12	1	17	0.08	0.731
Cannabis			10.30	1.42	24.21		**0.002**[b]
	Low vs placebo		4.18	1	17	0.44	0.057
	High vs placebo		13.07	1	17	0.66	**0.002**
	Low vs high		13.56	1	17	0.67	**0.002**
Alcohol*cannabis			1.32	2	34		0.282

Continued on page 860

Table 3. Effects of alcohol, cannabis, and alcohol*cannabis combination on blood cannabinoid pharmacokinetic parameters.[a]
(Continued from page 859)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
THCCOOH-glucuronide							
C_{max}							
Alcohol		19	0.50	1	18	0.16	0.490
Cannabis			16.46	1.46	26.31		**<0.001**[b]
	Low vs placebo		29.64	1	18	0.79	**<0.001**
	High vs placebo		31.94	1	18	0.80	**<0.001**
	Low vs high		0.15	1	18	0.09	0.443
Alcohol*cannabis			0.34	2	36		0.712
$C_{max\text{-}BL}$							
Alcohol		18	1.03	1	17	0.24	0.325
Cannabis			17.98	2	34		**<0.001**
	Low vs placebo		14.27	1	17	0.68	**0.002**
	High vs placebo		27.96	1	17	0.79	**<0.001**
	Low vs high		8.52	1	17	0.58	**0.010**
Alcohol*cannabis			1.18	2	34		0.318
t_{max}							
Alcohol		11	5.36	1	10	0.59	**0.043**
Cannabis			0.58	2	20		0.567
	Low vs placebo		0.05	1	10	0.07	0.834
	High vs placebo		0.44	1	10	0.21	0.522
	Low vs high		1.51	1	10	0.36	0.248
Alcohol*cannabis			0.25	2	20		0.780
t_{last}							
Alcohol		11	3.07	1	10	0.48	0.110
Cannabis			5.62	1.02	10.24		**0.038**[b]
	Low vs placebo		6.07	1	10	0.61	**0.033**
	High vs placebo		5.28	1	10	0.59	**0.044**
	Low vs high		0.61	1	10	0.24	0.455
Alcohol*cannabis			1.74	1.06	10.63		0.216[b]
$AUC_{0\text{-}8.3h}$							
Alcohol		19	0.15	1	18	0.09	0.704
Cannabis			17.25	1.48	26.58		**<0.001**[b]
	Low vs placebo		37.23	1	18	0.82	**<0.001**
	High vs placebo		30.36	1	18	0.79	**<0.001**
	Low vs high		1.67	1	18	0.29	0.212
Alcohol*cannabis			0.66	1.52	27.36		0.487[b]
$AUC_{>BL\text{-}8.3h}$							
Alcohol		18	0.30	1	17	0.13	0.591
Cannabis			15.07	2	34		**<0.001**
	Low vs placebo		8.93	1	17	0.59	**0.008**
	High vs placebo		20.68	1	17	0.74	**<0.001**
	Low vs high		10.77	1	17	0.62	**0.004**
Alcohol*cannabis			1.56	2	34		0.225

[a] Data from 19 occasional to moderate cannabis smokers who participated in all dosing sessions (lower n reflects fewer participants with calculable ANOVA results because of negative placebo samples). See online Supplemental Table 3 for C_{last} and THC-glucuronide, cannabidiol, and cannabinol data. Statistical analysis performed by factorial repeated-measures analysis of variance. Bold type indicates statistical significance at $P < 0.05$. Cannabis was administered with Volcano Medic vaporizer: 500 mg placebo [0.008% (0.002%) THC], low-dose [2.9% (0.14%) THC], or high-dose [6.7% (0.05%) THC] THC. Active alcohol dose was calculated to produce approximate 0.065% peak breath alcohol concentration.
[b] Mauchly test showed sphericity was violated on main effects, so Greenhouse–Geisser correction was used.
[c] Placebo doses not included in ANOVA because of too few positive specimens for comparison.

Table 4. Effects of alcohol, cannabis, and alcohol*cannabis combination on plasma cannabinoid pharmacokinetic parameters.[a]

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
THC							
C_{max}							
Alcohol		19	5.20	1	18	0.47	**0.035**
Cannabis			40.28	1.17	20.99		**<0.001**[b]
	Low vs placebo		143.53	1	18	0.94	**<0.001**
	High vs placebo		53.52	1	18	0.87	**<0.001**
	Low vs high		13.05	1	18	0.65	**0.002**
Alcohol*cannabis			1.72	1.19	21.47		0.205[b]
$C_{max\text{-}BL}$							
Alcohol		18	5.32	1	17	0.49	**0.034**
Cannabis			37.64	1.19	20.25		**<0.001**[b]
	Low vs placebo		105.24	1	17	0.93	**<0.001**
	High vs placebo		50.14	1	17	0.86	**<0.001**
	Low vs high		13.99	1	17	0.67	**0.002**
Alcohol*cannabis			3.08	1.22	20.69		0.088[b]
t_{max}							
Alcohol		11	4.53	1	10	0.56	0.059
Cannabis			4.75	1.00	10.01		0.054[b]
	Low vs placebo		4.85	1	10	0.57	0.052
	High vs placebo		4.66	1	10	0.56	0.056
	Low vs high		0.24	1	10	0.15	0.636
Alcohol*cannabis			4.43	1.00	10.01		0.062[b]
t_{last}							
Alcohol		11	0.02	1	10	0.04	0.890
Cannabis			6.43	1.16	11.55		**0.024**[b]
	Low vs placebo		6.64	1	10	0.63	**0.028**
	High vs placebo		6.89	1	10	0.64	**0.025**
	Low vs high		0.00	1	10	0.01	0.981
Alcohol*cannabis			1.65	2	20		0.216
$AUC_{0\text{-}8.3h}$							
Alcohol		19	1.35	1	18	0.26	0.261
Cannabis			4.09	1.00	18.05		0.058[b]
	Low vs placebo		245.38	1	18	0.97	**<0.001**
	High vs placebo		5.13	1	18	0.47	**0.036**
	Low vs high		2.53	1	18	0.35	0.129
Alcohol*cannabis			1.26	1.00	18.04		0.277[b]
$AUC_{>BL\text{-}8.3h}$							
Alcohol		18	1.39	1	17	0.27	0.255
Cannabis			42.73	1.15	19.57		**<0.001**[b]
	Low vs placebo		144.09	1	17	0.95	**<0.001**
	High vs placebo		54.40	1	17	0.87	**<0.001**
	Low vs high		15.63	1	17	0.69	**0.001**
Alcohol*cannabis			1.49	1.24	21.03		0.242[b]

Continued on page 862

Table 4. Effects of alcohol, cannabis, and alcohol*cannabis combination on plasma cannabinoid pharmacokinetic parameters.[a]
(Continued from page 861)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
11-OH-THC							
C_{max}							
Alcohol		19	6.12	1	18	0.50	**0.024**
Cannabis			31.30	1.22	21.90		**<0.001**[b]
	Low vs placebo		73.17	1	18	0.90	**<0.001**
	High vs placebo		39.70	1	18	0.83	**<0.001**
	Low vs high		12.24	1	18	0.64	**0.003**
Alcohol*cannabis			2.77	1.34	24.15		0.100[b]
$C_{max\text{-}BL}$							
Alcohol		18	3.31	1	17	0.40	0.087
Cannabis			33.26	1.23	20.88		**<0.001**[b]
	Low vs placebo		60.95	1	17	0.88	**<0.001**
	High vs placebo		41.89	1	17	0.84	**<0.001**
	Low vs high		15.74	1	17	0.69	**0.001**
Alcohol*cannabis			3.57	1.49	25.30		0.055[b]
t_{max}							
Alcohol	Low vs high[c]	17	2.35	1	16	0.36	0.145
Cannabis	Low vs high[c]		0.13	1	16	0.09	0.724
Alcohol*cannabis	Low vs high[c]		0.17	1	16	0.10	0.683
t_{last}							
Alcohol	Low vs high[c]	17	3.37	1	16	0.42	0.085
Cannabis	Low vs high[c]		4.04	1	16	0.45	0.062
Alcohol*cannabis	Low vs high[c]		0.65	1	16	0.20	0.432
$AUC_{0\text{-}8.3h}$							
Alcohol		19	1.06	1	18	0.24	0.317
Cannabis			28.02	1.13	20.27		**<0.001**[b]
	Low vs placebo		75.29	1	18	0.90	**<0.001**
	High vs placebo		32.97	1	18	0.80	**<0.001**
	Low vs high		12.54	1	18	0.64	**0.002**
Alcohol*cannabis			1.92	1.21	21.73		0.179[b]
$AUC_{>BL\text{-}8.3h}$							
Alcohol		18	0.94	1	17	0.23	0.346
Cannabis			29.53	1.13	19.22		**<0.001**[b]
	Low vs placebo		82.54	1	17	0.91	**<0.001**
	High vs placebo		35.84	1	17	0.82	**<0.001**
	Low vs high		13.51	1	17	0.67	**0.002**
Alcohol*cannabis			1.10	1.40	23.85		0.327[b]
THCCOOH							
C_{max}							
Alcohol		19	0.01	1	18	0.03	0.910
Cannabis			26.04	1.52	27.30		**<0.001**[b]
	Low vs placebo		40.06	1	18	0.83	**<0.001**
	High vs placebo		49.99	1	18	0.86	**<0.001**
	Low vs high		4.78	1	18	0.46	**0.042**
Alcohol*cannabis			0.22	1.40	25.21		0.726[b]

Continued on page 863

Table 4. Effects of alcohol, cannabis, and alcohol*cannabis combination on plasma cannabinoid pharmacokinetic parameters.[a]
(Continued from page 862)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
$C_{max\text{-}BL}$							
Alcohol		18	0.65	1	17	0.19	0.431
Cannabis			44.15	1.15	19.50		**<0.001**[b]
	Low vs placebo		163.82	1	17	0.95	**<0.001**
	High vs placebo		55.51	1	17	0.87	**<0.001**
	Low vs high		14.56	1	17	0.68	**0.001**
Alcohol*cannabis			0.83	1.34	22.84		0.405[b]
t_{max}							
Alcohol		13	0.56	1	12	0.21	0.470
Cannabis			1.46	1.03	12.40		0.250[b]
	Low vs placebo		1.33	1	12	0.32	0.271
	High vs placebo		1.61	1	12	0.34	0.229
	Low vs high		0.82	1	12	0.25	0.383
Alcohol*cannabis			0.05	1.05	12.64		0.842[b]
t_{last}							
Alcohol		14	0.03	1	13	0.05	0.858
Cannabis			2.51	1.03	13.41		0.136[b]
	Low vs placebo		2.73	1	13	0.42	0.123
	High vs placebo		2.33	1	13	0.39	0.151
	Low vs high		0.56	1	13	0.20	0.467
Alcohol*cannabis			0.01	1.03	13.37		0.941[b]
$AUC_{0\text{-}8.3h}$							
Alcohol		19	0.17	1	18	0.10	0.689
Cannabis			19.47	2	36		**<0.001**
	Low vs placebo		22.40	1	18	0.74	**<0.001**
	High vs placebo		48.87	1	18	0.85	**<0.001**
	Low vs high		2.51	1	18	0.35	0.130
Alcohol*cannabis			0.05	1.35	24.23		0.886[b]
$AUC_{>BL\text{-}8.3h}$							
Alcohol		18	0.02	1	17	0.03	0.888
Cannabis			29.55	1.22	20.71		**<0.001**[b]
	Low vs placebo		81.28	1	17	0.91	**<0.001**
	High vs placebo		39.24	1	17	0.84	**<0.001**
	Low vs high		9.85	1	17	0.61	**0.006**
Alcohol*cannabis			0.25	1.19	20.16		0.662[b]
THCCOOH-glucuronide							
C_{max}							
Alcohol		19	0.89	1	18	0.22	0.358
Cannabis			20.03	2	36		**<0.001**
	Low vs placebo		19.77	1	18	0.72	**0.001**
	High vs placebo		28.55	1	18	0.78	**<0.001**
	Low vs high		7.93	1	18	0.55	**0.011**
Alcohol*cannabis			0.95	2	36		0.397

Continued on page 864

Table 4. Effects of alcohol, cannabis, and alcohol*cannabis combination on plasma cannabinoid pharmacokinetic parameters.[a]
(Continued from page 863)

Analyte and parameter	Cannabis dose (pairwise comparison)	n	*F*	*df*	Error *df*	Effect size, *r*	*P*
$C_{max\text{-}BL}$							
Alcohol		18	0.10	1	17	0.08	0.759
Cannabis			18.67	2	34		**<0.001**
	Low vs placebo		35.79	1	17	0.82	**<0.001**
	High vs placebo		33.41	1	17	0.81	**<0.001**
	Low vs high		1.91	1	17	0.32	0.185
Alcohol*cannabis			0.82	1.36	23.10		0.410[b]
t_{max}							
Alcohol		12	1.07	1	11	0.30	0.323
Cannabis			0.35	2	22		0.712
	Low vs placebo		0.11	1	11	0.10	0.751
	High vs placebo		0.55	1	11	0.22	0.474
	Low vs high		0.27	1	11	0.16	0.612
Alcohol*cannabis			0.57	2	22		0.574
t_{last}							
Alcohol		12	0.16	1	11	0.12	0.693
Cannabis			1.04	2	22		0.371
	Low vs placebo		2.44	1	11	0.43	0.147
	High vs placebo		0.00	1	11	0.01	0.975
	Low vs high		2.12	1	11	0.40	0.173
Alcohol*cannabis			0.00	2	22		0.998
$AUC_{0\text{–}8.3h}$							
Alcohol		19	0.88	1	18	0.22	0.362
Cannabis			11.87	1.23	22.16		**0.001**[b]
	Low vs placebo		22.55	1	18	0.75	**<0.001**
	High vs placebo		18.63	1	18	0.71	**<0.001**
	Low vs high		4.59	1	18	0.45	**0.046**
Alcohol*cannabis			1.21	1.38	24.87		0.299[b]
$AUC_{>BL\text{–}8.3h}$							
Alcohol		18	2.60	1	17	0.36	0.125
Cannabis			15.76	2	34		**<0.001**
	Low vs placebo		26.93	1	17	0.78	**<0.001**
	High vs placebo		24.79	1	17	0.77	**<0.001**
	Low vs high		3.23	1	17	0.40	0.090
Alcohol*cannabis			0.40	1.45	24.62		0.609[b]

[a] Data from 19 occasional to moderate cannabis smokers who participated in all dosing sessions (lower n reflects fewer participants with calculable ANOVA results because of negative placebo samples). See online Supplemental Table 4 for C_{last} and THC-glucuronide, cannabidiol, and cannabinol data. Statistical analysis performed by factorial repeated-measures ANOVA. Bold type indicates statistical significance at $P < 0.05$. Cannabis was administered with Volcano Medic vaporizer: 500 mg placebo [0.008% (0.002%) THC], low-dose [2.9% (0.14%) THC], or high-dose [6.7% (0.05%) THC] THC. Active alcohol dose was calculated to produce approximate peak 0.065% peak breath alcohol concentration.
[b] Mauchly test showed sphericity was violated on main effects, so Greenhouse–Geisser correction was used.
[c] Placebo doses not included in ANOVA because of too few positive specimens for comparison.

Thus, our 0.42-h postdose time is comparable to Desrosiers' 0.5 h, producing median (range) THC of 10.0 (1.6–17.9) μg/L (L) and 13.2 (2.4–40.8) μg/L (H) and better illustrating differences between occasional and frequent smokers. An occasional smoker cohort had THC C_{max} 12.1 (4.1–40.3) μg/L *(16)*, similar to our approximately 0.5 h findings. The only prior direct comparison of cannabis vaporization and smoking examined within-

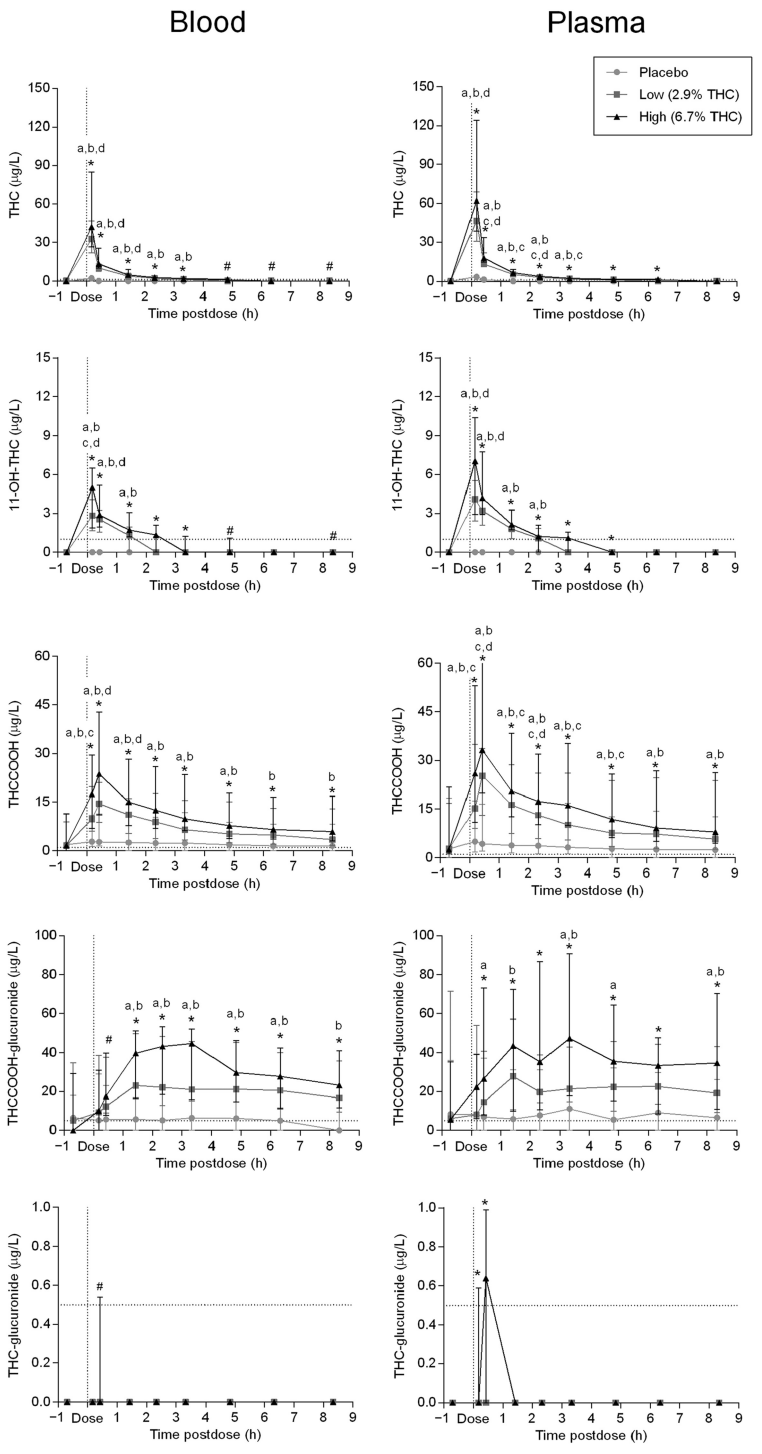

Fig. 1. Median (interquartile range) blood and plasma cannabinoids after cannabis vaporization (n = 19).

THC content: placebo 0.008% (0.002%), low 2.9% (0.14%), high 6.7% (0.05%). Horizontal dotted line indicates analyte limit of quantification. * Overall $P < 0.006$ (Friedman ANOVA), n = 19. # Overall $P < 0.05$. [a] $P < 0.006$ (placebo vs high, no alcohol). [b] $P < 0.006$ (placebo vs high, with alcohol). [c] $P < 0.006$ (placebo vs low, no alcohol). [d] $P < 0.006$ (placebo vs low, with alcohol). [e] $P < 0.006$ (low vs high, no alcohol). [f] $P < 0.006$ (low vs high, alcohol).

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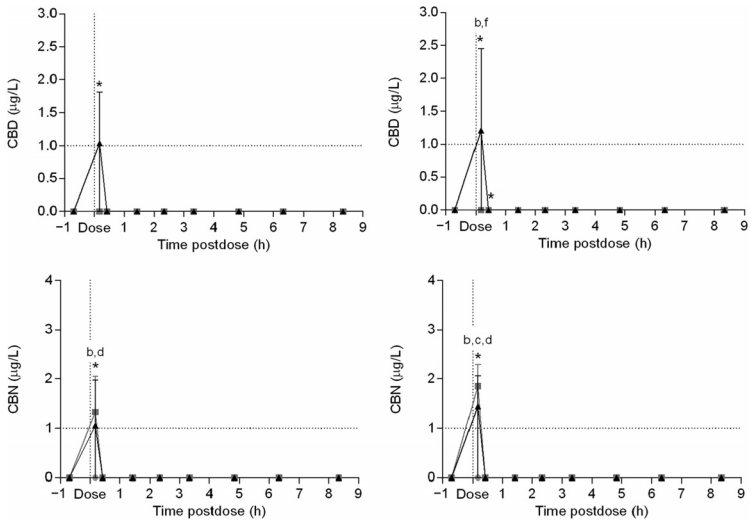

Fig. 1. Continued.

individual plasma THC after 1.7%, 3.4%, and 6.8% THC *(11)*. Cigarettes were halved; half were smoked, the other half vaporized. The 2 routes produced similar plasma THC concentrations and 6-h AUCs. Pulmonary THC intake after vaporization is similar to smoking *(22)*, with approximately 54% of the THC dose delivered to the balloon for inhalation, and 30%–40% exhaled. Smoking cannabis also has factors that decrease THC delivery relative to dose. Approximately 23%–30% of THC is lost by pyrolysis and 40%–50% as sidestream smoke *(23)*. Our blood and plasma study corroborates evidence that vaporization is an effective alternative administration route (mitigating health concerns from combustion byproduct inhalation due to the lower vaporization temperature), delivering THC in a similar manner to smoking and producing similar cannabinoid concentration profiles.

Participants inhaled ad libitum by controlling inhalation rate, depth, and hold time in the lungs (inhalation topography, allowing individual self-titration on the basis of pharmacological response) *(24)*, contributing to substantial interindividual variability in cannabinoid concentration profiles. Significantly higher C_{max} and $AUC_{0-8.3h}$ were observed for THC, THC-glucuronide, 11-OH-THC, THCCOOH, THCCOOH-glucuronide (only when accounting for baseline), and CBD after H vs L cannabis. However, 52.6% of completers' within-individual blood THC C_{max} values indicated self-titration: 21.0% had L and H C_{max} values within 20% of each other for ≥1 alcohol condition, and 31.6% had higher C_{max} values after L than H doses. For most compounds, noticeable median/range differences for the same THC potency with (+) and without (−) alcohol (Table 2 and online Supplemental Table 2) generally occurred only after the H dose; L doses produced consistent C_{max} and AUCs. This also supports self-titration: participants required less self-titration at the L dose to achieve intended results, likely consuming the full amount. More variability after the H dose suggests greater self-titration. Apart from inhalation topography, factors affecting vaporized THC delivery include heating temperature, number of balloon fillings, cannabis amount and blend, and length of time between volatilization and inhalation (owing to possible THC adherence to the balloon) *(12, 22, 25)*.

Most previous cannabis and alcohol concentrations were reported from roadside drugged driving prevalence studies, providing no information about possible cannabinoid pharmacokinetic differences with alcohol *(8)*. Some controlled-administration experiments provided limited cannabis and alcohol pharmacokinetic data in relation to performance impairment assessments *(26–27)*. We showed significantly higher THC C_{max} with alcohol in blood and plasma, and additionally for other cannabinoids. Alcohol-cannabis interactions were statistically significant in blood 11-OH-THC C_{max}, but not plasma, limiting conclusions from this observation. One study *(28–29)* directly examined combined alcohol and cannabis pharmacokinetics in chronic smokers; but with only 1 cannabis dose (400 μg/kg THC) and 3 alcohol conditions (placebo, approximately 0.05%, and approximately 0.07% blood alcohol concentration). Alcohol before smoking did not significantly affect THC C_{max} *(28–29)*. Similar results were reported in another study, which also found no significant differences in plasma THC C_{max} or AUC after ingesting 420 and 850 mg/kg alcohol vs placebo alcohol (cannabis smoked 0.25 h post-

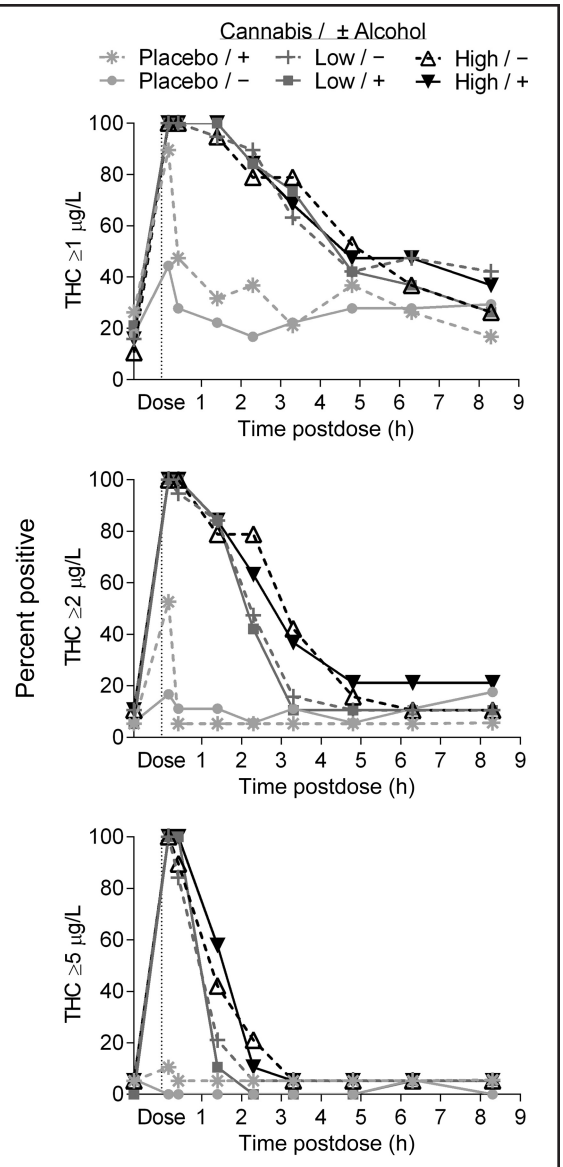

Fig. 2. Percent completers (n = 19) positive for THC in whole blood for various cutoffs after controlled administration of vaporized cannabis [placebo, low (2.9%), and high (6.7%) THC] and alcohol (placebo and active).

alcohol) *(30)*. Plasma THC increased nonsignificantly but dose-dependently with increasing alcohol. Plasma THC 0.3 h postsmoking was "generally higher" 0.8 h after alcohol than without alcohol *(26)*, but no statistics were provided. Moderate alcohol (0.35 g/kg) produced significantly higher plasma THC within 15 min after start of smoking, but significant differences were not observed over a full 90-min THC curve *(31)*. In contrast, 0.7 g/kg alcohol produced significantly lower serum THC 1 h postsmoking *(28)*. Generally, these results corroborate ours, as observed THC C_{max} occurred immediately postinhalation (within 15 min).

Because alcohol increased THC and 11-OH-THC C_{max} but not $AUC_{0-8.3h}$ (even accounting for baseline), it is possible that alcohol affected absorption (higher concentrations immediately postinhalation). Possible alcohol-induced perfusion and distribution changes affect other drugs *(28, 32)*. Acute alcohol increases cardiac output within 30 min *(33)*, possibly leading to more rapid THC absorption during inhalation due to increased pulmonary capillary flow. In contrast to prior studies with a time delay (≥0.3 h) between alcohol and cannabis to allow for alcohol absorption *(26–29, 31)*, the present experiment administered cannabis and alcohol concurrently; the entire dosing process required ≤20 min. Our approach retains real-world validity for recreational intake. It is also possible that our higher blood cannabinoid C_{max} reflects less careful cannabis self-titration after alcohol.

Overall, we observed minimal alcohol effects on THC metabolism. Higher blood and plasma 11-OH-THC C_{max} values (Table 2) could be due to increased metabolism, but probably result from higher THC C_{max}. Blood THCCOOH-glucuronide C_{max} occurred earlier with alcohol (+), but plasma THCCOOH-glucuronide C_{max} did not. Nonglucuronidated THCCOOH t_{max} was unaffected by alcohol or cannabis condition in either matrix. Although the alcohol-cannabis interaction on metabolite 11-OH-THC t_{last} in blood was statistically significant, it was based only on L and H cannabis doses (too many negative samples after placebo) and no clear pattern emerged. Thus, it does not appear to be clinically significant. No alcohol differences emerged at specific collection times, and there were no alcohol effects on THCCOOH concentrations. Limited other data are available on alcohol effects on cannabinoid metabolites *(28–29)*. Although lower THCCOOH was observed after alcohol than placebo alcohol over 4 h *(28)*, the effect was not significant owing to interindividual variability from prior cannabis smoking history. Our observations were similar (see online Supplemental Figs. 1 and 2).

Participants 7, 13, and 22 had ≥10 μg/L blood THCCOOH and ≥40 μg/L blood THCCOOH-glucuronide at baseline in ≥4 sessions and ≥1 baseline blood THC ≥1.4 μg/L. Participant 7 additionally had 1 session with baseline 11-OH-THC 1.0 μg/L. In all 6 sessions, participants 9 and 31 had ≥72.4 μg/L baseline THCCOOH-glucuronide, ≥17.9 μg/L THCCOOH, and ≥1.4 μg/L THC. These 5 participants were likely the most frequent smokers in our cohort. Fabritius et al. *(34)* recently proposed that free blood THCCOOH thresholds differentiated occasional (≤3 μg/L) from frequent (≥40 μg/L) cannabis smokers, although 38.7% of occasional smokers' samples had THCCOOH >3 μg/L

and 83.6% of frequent smokers' samples had THCCOOH ≤40 μg/L. By these criteria, 52.6% of our completers would be considered occasional smokers; the others fell between categories. Other factors in THCCOOH and THCCOOH-glucuronide interpretation include metabolism time and residual cannabinoids (acute vs chronic exposure). Observed THCCOOH-glucuronide t_{max} occurred later (median ≥1.4 h) than THCCOOH t_{max} (median <0.5 h) (Table 2), owing to the additional phase II metabolic process. THCCOOH and THCCOOH-glucuronide median and range concentration values were considerably lower when accounting for baseline, highlighting the effect of residual cannabinoid presence. THCCOOH-glucuronide/THCCOOH ratios and variability (see online Supplemental Fig. 5) were similar to after smoking in occasional smokers *(16)*.

This study has multiple strengths. With extensive vaporized cannabis pharmacokinetic data, we confirm the utility of vaporization as a viable and effective cannabis-smoking alternative. We also characterize cannabinoid blood and plasma pharmacokinetics with concurrent alcohol, by use of gray-top Vacutainers, the collection device most commonly used in forensic settings. Alcohol effects on cannabinoid pharmacokinetics are of interest due to the commonality of coingestion. Combining these drugs affects performance impairment *(5)*, possibly in part owing to higher cannabinoid concentrations. Our data provide a valuable pharmacokinetic reference for clinicians regarding future therapeutic use of vaporized cannabis. We also explicitly illustrate individual variability in inhalation behavior, documenting evidence of self-titration in half of participants. Increasing THC potency affects people differently, depending on cannabis use history. An additional strength is inclusion of phase II THC- and THCCOOH-glucuronides, as well as minor cannabinoids CBD and CBN. Limited blood and plasma controlled-administration data exist for these compounds *(15–17, 35)*. Metabolites provide valuable information on smoking history and time since last intake *(34, 36)*. No study to date examined phase II metabolites after vaporization and alcohol; these data improve blood and plasma interpretation by toxicologists as medical and recreational cannabis prevalence expands. THC-glucuronide is detected at low concentrations, within 0.5 h postsmoking. CBD and CBN were not detected after 0.42 h in this study, so these compounds have utility as recent-use markers in blood. No known study to date detected CBD or CBN in blood or plasma after 2.1 h postinhalation *(15–16)*, although controlled smoked administration studies usually contained low (≤1 mg) CBD and CBN doses. Blood collection may be delayed after an accident or traffic stop *(37)*, making it unlikely that these compounds will be detected. Karschner et al. *(35)* reported CBD t_{max} 1.0–5.5 h after Sativex (1:1 CBD:THC oromucosal spray, 5 and 15 mg CBD). This result highlights CBD relevance in forensic cannabinoid testing, given increasing medical cannabis prevalence. We recommend controlled administration studies of smoked and vaporized high-CBD cannabis strains, used for antiepileptic, antiemetic, antiinflammatory, and antipsychotic effects *(38–39)*.

Study limitations include blood and plasma collections for only 8.3 h. Additionally, we did not directly compare vaporized cannabis to smoking to fully evaluate relative bioavailability. This investigation focused on participants with self-reported occasional to moderate cannabis intake histories; additional research is needed to characterize vaporized cannabis and alcohol pharmacokinetics in chronic frequent smokers.

Different THC cutoffs yielded different positivity rates (Fig. 2). At 1 μg/L, THC was positive in ≥42.1% of participants 4.8 h after active (L and H) and ≥27.8% after placebo, owing to residual THC from previous self-administration. With THC ≥2 μg/L, 10.5%–15.8% were positive 3.3 h after L and 36.8%–42.1% after H doses. THC ≥5 μg/L cutoffs resulted in only 1 THC-positive participant at 3.3 h. We expect positivity rates to be higher and for longer postvaporization in frequent smokers *(6)*, thus warranting investigation. These debated per se cutoffs yield different detection windows in these occasional to moderate smokers, with 2 μg/L limiting the window to approximately 4.8 h postdose (Fig. 2), similar to the window of acute intoxication *(40)*. A higher 5-μg/L cutoff results in a short detection window for occasional to moderate smokers—shorter than impairment windows *(5, 40)*—emphasizing the challenge in establishing appropriate science-based per se cannabis drugged driving legislation.

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