K53 Blood Cannabinoid Pharmacokinetics in Frequent Cannabis Smokers After Controlled Smoked, Vaporized, and Oral Cannabis Administration: Markers of Recent Cannabis Intake

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After attending this presentation, attendees will be able to describe the blood pharmacokinetics of Δ^9-Tetrahydrocannabinol (THC), its metabolites, and minor cannabinoids after controlled smoked, vaporized, and oral administration in frequent cannabis smokers.

This presentation will impact the forensic science community by aiding in the interpretation of blood cannabinoid results after three different administration routes within the same participants.

Cannabis is the most commonly reported illicit drug in motor vehicle crashes and fatalities. THC is rapidly distributed into highly perfused organs and later into adipose tissue. With frequent cannabis intake, a large body burden of THC is achieved that slowly re-enters the bloodstream, such that positive blood cannabinoid results are observed hours after the window of acute impairment, complicating cannabinoid result interpretation. There is increasing interest in whether unique cannabinoid markers (cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), Δ9-tetrahydrocannabivarin (THCV), 11-nor-9-carboxy-THCV (THCVCOOH), and THC-glucuronide) can identify recent cannabis intake after it is smoked, vaporized, and/or ingested. Direct comparison of cannabinoid pharmacokinetics in the same population after different administration routes has not been investigated.

Seven frequent (≥5x/week) cannabis smokers participated in this National Institute on Drug Abuse Institutional Review Board, Food and Drug Administration (FDA), and Drug Enforcement Administration (DEA) -approved study; all provided written informed consent. Participants entered the secure research unit approximately 19h prior to dosing. The study was conducted with a double-blind, crossover, and placebo-controlled design consisting of four sessions that were randomized, including a double-placebo session. Participants consumed a placebo or active oral (baked in a brownie) cannabis dose (6.9% THC), followed by placebo or active smoked or vaporized cannabis. Only one administration route had active THC in each session. Smoking, inhaling, and eating occurred *ad libitum* for 10min. Blood was collected prior to, during, and up to 72h after dosing. THC, 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), CBD, CBN, CBG, THCV, THCVCOOH, THC-glucuronide, and THCCOOH-glucuronide concentrations were quantified by Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS). Wilcoxon signed-rank tests were performed to compare median pharmacokinetic parameters between administration routes (two-tailed $p<0.05$ significance threshold).

A total of 189 blood specimens were collected for each active administration route. THC was quantifiable in all specimens collected after smoking and oral dosing, and 92.1% after vaporization (THC only up to 5h post-dose in one participant). 11-OH-THC was measureable in 64.6%-70.9% of specimens and THCCOOH in all specimens. Median THC, 11-OH-THC, and THCCOOH times (t_{max}) of maximum observed concentrations (C_{max}) were 2.5h after oral dosing and occurred significantly later than after smoking (0.10h, 0.20h, and 0.25h, respectively) or vaporization (0.10h, 0.17h, and 0.25h, respectively). Median THC C_{max} was significantly greater after smoking (117µg/L) and vaporization (98.0µg/L) than oral dosing (15.6µg/L). Median THCCOOH C_{max} after oral dosing (75.2µg/L) was significantly greater than after vaporization (29.5µg/L). THCCOOH-glucuronide was quantifiable in all specimens after smoking and oral dosing, and 91.5% after vaporization; THCCOOH was detected longer than THCCOOH-glucuronide after vaporization due to differences in limits of quantification. CBD, CBN, CBG, and THCV were only observed after smoking and vaporization (7.4%-30.2%); median last detection times (t_{last}) were 0.17h-0.5h, except for 1.5h after smoking for CBN. THCVCOOH was measured in 10.6%-21.7% of specimens after all doses, but only in all participants after oral doses. THCVCOOH was first quantified a median of 1.5h after oral dosing, but detectable for as long as 26h. THC-glucuronide was quantifiable in 1.6% of specimens after smoking (t_{last} 0.5h) and 3.2% after oral (t_{last} 2.5h) cannabis.

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Cannabinoid pharmacokinetics after smoking and vaporization were similar, but significantly different from oral dosing. CBN, CBG, and THCV were good markers of recent cannabis smoking and vaporization when identified, but were not measureable in all participants. THC-glucuronide was present in fewer specimens than other markers, but detected after oral dosing when others were not. Presence of CBN, CBG, THCV, or THC-glucuronide identified cannabis intake within 2.5h after any route of administration, but absence of any of these markers did not preclude recent cannabis use. These data improve identification of recent cannabis intake and improve interpretation of blood cannabinoid results.

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