Evaluation of the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking

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Abstract

Background
Cannabis is the most commonly reported illicit drug in drugged driving cases. Achieving accurate oral fluid (OF) cannabinoid on-site results is challenging and essential.

Aims
Device performance and OF cannabinoid detection windows 30h post-smoking were evaluated in occasional (<2x/week) and frequent (≥4x/week) cannabis smokers.

Methods
10 occasional and 14 frequent smokers (18-45 years) provided written informed consent for this Institutional Review Board-approved study, and smoked *ad libitum* one 6.8% THC cannabis cigarette. OF was collected with the DrugTest 5000 test cassette and Oral-Eze® collector (Quest Diagnostics) before and frequently up to 30h post-dose. Test cassettes were analyzed immediately and compared to two-dimensional gas chromatography mass spectrometry (2D-GCMS) cannabinoid results from simultaneously collected Oral-Eze OF.

Results
404 paired OF were collected; 9 samples (2.2%) were invalid, yielding 395 OF pairs for comparison. Sensitivity, specificity and efficiency were 75.3, 94.1, and 81.8% and 66.4, 98.9, and 73.9% with 2 ng/mL THC proposed SAMHSA and 1 ng/mL DRUID confirmation cutoffs, respectively. Sensitivity was 6-11% higher in chronic frequent as compared to occasional cannabis smokers due to longer detection windows and higher true positive rates. Median (range) last detection times with the DrugTest 5000 were 12h (4-24) and 21h (1->30) for occasional and frequent smokers, respectively (p=0.12, >30 assigned as 30h). Three frequent smokers were still positive at 30h, but had up to 5 negative specimens prior to 30h.

Discussion and conclusions
Sensitivity of the DrugTest 5000 5 ng/mL cutoff was lower for occasional as compared to chronic frequent smokers over the extended 30h monitoring window with the 2 and 1 ng/mL confirmation cutoffs; however, these authentic data after controlled smoking document the best performance to date for on-site cannabinoid tests. Sensitivity within 6 and 8h time frames, representing recent smoking, were 85.6 and 84.7%; and 84.0 and 82.5% at the proposed SAMHSA and DRUID confirmation cutoffs, respectively.

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Introduction
Cannabis sativa (marijuana) has been smoked for its medicinal and psychoactive properties for thousands of years and is the most widely consumed illicit drug in the world (Vega et al.,

2002). Worldwide, 119-224 million people (2.6-5.0%) aged 15-64 consumed cannabis at least once in 2010 (World Drug Report 2012). In 2011 in the United States, 18.1 million Americans 12 years and older (7.0%) reported past-month use and 4.3 million Americans (1.6%) reported past-year cannabis dependence or abuse (Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. 2012). In addition, 872,000 Americans received treatment for cannabis dependence or abuse, second only to alcohol. Cannabis is also common in driving under the influence of drugs (DUID) cases. Δ^9-tetrahydrocannabinol (THC) was the most prevalent illicit drug detected in injured drivers (9.8%) in Victoria, Australia (Drummer, Kourtis, Beyer, Tayler, Boorman, Gerostamoulos, 2012). Similarly, in the first US Roadside Survey in 2007, cannabinoids were identified in oral fluid and/or blood in 8.6% of nighttime drivers (Lacey et al., 2009). Nearly two-thirds of U.S. trauma center admissions were due to motor vehicle accidents, with almost 60% positive for drugs or alcohol (Walsh et al., 2004). Acute cannabis intoxication produces dose-related impairment in cognitive and psychomotor functioning, as well as risk-taking behavior (McDonald, Schleifer, Richards, de Wit H., 2003); Ramaekers et al., 2006). Reaction time (RT), perception, short-term memory and attention, motor skills, tracking, and skilled activities are altered (Ramaekers, Berghaus, van Laar, Drummer, 2004; Riedel and Davies, 2005). Driving within one hour of smoking cannabis increased crash risk (odds ratio (OR) 1.84 (Asbridge, Poulin, Donato, 2005) and 2.61 (Mann et al., 2007), even after adjustment for demographic characteristics. In France, drivers in fatal crashes with detectable THC in blood had a 3.17 OR for crash responsibility (Laumon, Gadegbeku, Martin, Biecheler; SAM Group, 2005). Driving under the influence of cannabis or synthetic cannabinoids prior to or during driving increases the risk of death or injury and is an important public safety concern.

Oral fluid drug testing in workplace, pain management, drug treatment and DUID programs is increasing due to advantages in drug monitoring including easy, less invasive specimen collection, lack of the need for a same-sex collector, and less opportunity for adulteration. Elucidating cannabinoid oral fluid pharmacokinetics after controlled smoked cannabis is essential for determining drug detection windows, markers of recent smoking, and minimizing potential for passive environmental smoke contamination. The ideal drug detection window varies depending upon the goals and design of drug testing programs. For workplace, pain management, and drug treatment research follow-up visits, a long drug detection window is ideal, as testing opportunities are widely separated. However, drug testing during accident investigations or "for cause" testing is focused on recent use and potential impairment. Controlled cannabis administration and sequestration of participants on closed research units to eliminate self-administered drugs provide data for rigorously determining windows of drug detection in oral fluid and improving result interpretation. Oral fluid testing offers non-invasive sample collection for on-site drug testing; however, until recently (Desrosiers et al., 2012), test performance for THC detection had unacceptable diagnostic sensitivity. On-site tests must accurately identify cannabis exposure since this drug accounts for the highest prevalence in workplace drug testing and DUID programs. The DrugTest 5000 on-site device provided high diagnostic sensitivity and specificity for detection of cannabinoid exposure.

We conducted a controlled smoked cannabis administration study are to characterize and contrast the disposition of THC and its metabolites in blood, plasma, urine, oral fluid, and breath in occasional and chronic frequent cannabis smokers. In addition, we evaluated the sensitivity, specificity, accuracy, and predictive values of the Draeger DrugTest 5000® for identifying cannabinoids in oral fluid as compared to cannabinoid results when oral fluid was

collected with the Oral-Eze collector (Quest Diagnostics) before and frequently up to 30 hours after smoking a 6.8% THC cigarette.

Methods

Study Design

This clinical study, approved by the National Institute on Drug Abuse Institutional Review Board, recruited chronic frequent cannabis and occasional smokers. The study consisted of a three day, two-night stay on a closed clinical research unit. Baseline measures and biological samples were collected before drug administration. Participants smoked ad-libitum (10 min maximum) one 6.8±0.2% (54 mg) THC, 0.25±0.08 cannabidiol (CBD), and 0.21±0.02% cannabinol (CBN) cannabis cigarette the morning of Day 2 and provided oral fluid samples up to 30 hours after smoking.

Participants

Occasional and chronic frequent cannabis smokers (age 18-45 years) were recruited from the community by advertising and word-of-mouth. Occasional smokers self-reported an average smoking frequency <2 times per week in the past 3 months. Chronic frequent smokers self-reported an average smoking frequency ≥4 times per week in the past 3 months and had a positive urine cannabinoid test. Additional inclusion criteria included peripheral veins suitable for venipuncture, blood pressure ≤140 mm Hg systolic and 90 mm Hg diastolic, heart rate ≤90 bpm, and an electrocardiogram and 3-minute rhythm strip without clinically significant abnormalities. Exclusion criteria included history of any clinically significant illness, based on medical history, physical examination, and clinical laboratory tests, history of a clinically significant adverse event associated with cannabis intoxication, donation of more than 450 mL blood in previous 30 days, pregnancy or nursing, or interest or participation in drug abuse treatment within the past 60 days. Pregnancy tests were administered at screening and on the morning of drug administration to women with reproductive potential. The National Institute on Drug Abuse Institutional Review Board approved the study. All participants provided written informed consent and were compensated for their study participation.

Sample collection and analysis

The OralEze® device was utilized for oral fluid collection at admission (16 to 19 h before drug administration), 1 hour before, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10.5, 13.5, 21, 24, 26, 28, and 30 hours after smoked cannabis. Oral intake, including smoking, was prohibited 10 min before oral fluid collection. The collection device consists of an absorptive cotton pad, a volume adequacy indicator that turns blue upon collection of 1 mL oral fluid, and a plastic tube containing 2 mL stabilizing buffer, yielding a 1:3 oral fluid dilution. Following manufacturer recommendations, analytes were eluted from the pad at room temperature for at least 12 hours. Oral fluid analysis generally occurred within 24 h of collection. THC, 11-OH-THC, THCCOOH, CBN, and CBD were quantified by two-dimensional gas chromatography mass spectrometry (2D-GCMS) according to a previously published method (Milman, Barnes, Lowe, Huestis, 2005) with minor modifications: calibrators and quality controls were prepared with 0.25 mL blank oral fluid and 0.5 mL Oral-Eze® buffer, identical with the 1:3 dilution of authentic samples. Intra-assay imprecision was 1.0%-4.7%, inter-assay imprecision was <7.6%, and bias was 88.2%-110.1%. The following pad recoveries were

observed: THC, 42.5-48.8%; 11-OH-THC, 43.5-54.5%; THCCOOH, 68.1-86.2%; CBN, 35.6-58.7%; and CBD, 33.5-47.7%.

DrugTest 5000 on-site oral fluid monitoring device

The DrugTest 5000 consists of an analyzer, a test cassette, and buffer cartridge to determine if cocaine, opiates, benzodiazepines, cannabinoids, amphetamines, or methamphetamine are present in oral fluid above specified cutoffs. After the buffer cartridge and test cassette are inserted into the instrument, the analysis is automated and the cartridge is pushed onto the tip of the test cassette for the lateral flow immunoassay. Test cassettes were calibrated during production with fortified native oral fluid and the threshold for a positive result encoded on the test cassette. Objective results are displayed on a screen as "Positive", "Negative," or "Invalid". An invalid result occurs if the instrument detects improper lateral flow. THC results are acquired in 8.5 min, while other drugs are obtained in 5 min. The DrugTest 5000 test cassette was equipped with a polymeric non-compressible pad for oral fluid collection. Oral fluid was collected by swiping the test cassette on the tongue and side of the cheeks. Test cassettes were analyzed immediately and compared to 2D-GCMS cannabinoid results from simultaneously collected Oral-Eze oral fluid.

Data analysis

Qualitative oral fluid DrugTest 5000 cannabinoid results were evaluated against a pre-programmed 5 μg/L THC cutoff. True positive (TP, DrugTest 5000 and GC-MS positive), true negative (TN, DrugTest 5000 and GC-MS negative), false positive (FP, positive DrugTest 5000, but less than GC-MS specified cutoff) and false negative (FN, negative DrugTest 5000, but positive GC-MS at specified cutoff) results were calculated at 5 μg/L THC DrugTest 5000 screening cutoff and 1 (Driving Under the Influence of Drugs, Alcohol and Medicines, DRUID), and 2 (Substance Abuse and Mental Health Services Administration, SAMHSA) GC-MS THC confirmation cutoffs. Diagnostic sensitivity (100×(TP/[TP+FN])), diagnostic specificity (100×(TN/[TN+FP])), and efficiency (100×([TP+TN]/[TP+TN+FP+FN])) were calculated at one screening and multiple confirmation cutoffs. Rates of detection and windows of detection were evaluated with the DrugTest 5000 screen and different confirmation analytes and cutoffs.

Results

Fourteen chronic, frequent and 10 occasional cannabis smokers spent the night before smoking on the clinical unit to ensure that participants were not intoxicated at the time of smoking. Chronic, frequent users reported smoking a median (range) of 28 cannabis joints per week (21-147), while occasional smokers reported 0.75 cannabis joints per week (0.06-2.5). Four hundred and four paired oral fluid specimens were collected; 9 samples (2.2%) were invalid, yielding 395 oral fluid pairs for comparison. Sensitivity, specificity and efficiency were 66.4, 98.9, and 73.9% with the 1 ng/mL DRUID, and 75.3, 94.1, and 81.8% with the 2 ng/mL THC proposed SAMHSA confirmation cutoffs, respectively. Sensitivity was 6-11% higher in chronic frequent as compared to occasional cannabis smokers due to longer detection windows and higher true positive rates. Median (range) last detection times with the DrugTest 5000 were 12 hours (4-24) and 21 hours (1->30) for occasional and frequent smokers, respectively (p=0.12, >30 assigned as 30 hours). Three frequent smokers'

oral fluid specimens were still positive at 30 hours, but had up to 5 negative oral fluid specimens prior to 30 hours.

Discussion and conclusions

The DrugTest 5000 was easy to operate and provided reliable results and operation. The instrument was designed to be operated by non-medical personnel in the field under diverse weather and lighting conditions. The oral fluid collection device has a volume indicator to tell the operator when sufficient oral fluid is collected. The device can only be inserted into the instrument in one way, and the reading of the reaction line is performed by the instrument, a major advantage over many other on-site tests that require the operator to read the presence or absence of a line to indicate a qualitative positive or negative test result. This is especially difficult under poor on-the-road lighting conditions.

Analysis of cannabinoids has been the major challenge to on-site oral fluid tests due primarily to poor sensitivity, although many other devices also had frequent false positive screening results. We previously reported sensitivity, specificity and efficiency of the Draeger DrugTest 5000 at a 5 ng/mL screening cutoff and 1 ng/mL DRUID (87.7%, 77.8% and 86.4%), and 2 ng/mL SAMHSA (90.7%, 75.0%, and 87.9%) 2D-GCMS analysis of oral fluid collected with the Quantisal oral fluid device in chronic frequent cannabis smokers. For the first time, we present performance data for the DrugTest 5000 5 ng/mL cutoff with the same confirmation cutoffs in oral fluid collected with the Oral-Eze collection device. Sensitivity of the DrugTest 5000 5 ng/mL cutoff was lower for occasional as compared to chronic frequent smokers over the extended 30 hours monitoring window with the 1 and 2 ng/mL confirmation cutoffs; however, these authentic data after controlled smoked cannabis document the best performance to date for on-site cannabinoid tests. Sensitivity within 6 and 8 hours time frames, highly relevant for DUID testing and representing recent cannabis smoking, were 85.6 and 84.7% and 84.0 and 82.5% at the proposed SAMHSA and DRUID confirmation cutoffs, respectively. These data document that a sensitive and specific on-site screening test for cannabinoids in oral fluid is available for use in DUID, workplace and drug treatment programs. The device is easy to use and produces reliable screening results. These data should advance the possibility of oral fluid testing for roadside testing, providing a deterrent for drugged driving, and a means of improving public health and safety.

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