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Residual cannabis levels in blood, urine and oral fluid following heavy cannabis use

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ABSTRACT

An understanding of tetrahydrocannabinol (THC) kinetics and residual levels after cannabis use is essential in interpreting toxicology tests in body fluids from live subjects, particularly when used in forensic settings for drug abuse, traffic and interpersonal violence cases. However the current literature is largely based on laboratory studies using controlled cannabis dosages in experienced users, with limited research investigating the kinetics of residual THC concentrations in regular high dose cannabis users. Twenty-one dependent cannabis users were recruited at admission to two residential detoxification units in Melbourne, Australia. After being provided with information about, and consenting to, the study, subjects volunteered to provide once-daily blood, urine and oral fluid (saliva) samples for seven consecutive days following admission, involving cessation and abstinence from all cannabis use. Blood and oral fluid specimens were analysed for THC and urine specimens for the metabolite THC-COOH. In some subjects THC was detectable in blood for at least 7 days and oral fluid specimens were positive for THC up to 78 h after admission to the unit. Urinary THC-COOH concentrations exceeded 1000 ng/mL for some subjects 129 h after last use. The presented blood THC levels are higher and persist longer in some individuals than previously described, our understanding and interpretation of THC levels in long term heavy cannabis users may need to be reconsidered.

1. Introduction

The interpretation of toxicological drug assays is often questioned in criminal proceedings. Our well-accepted knowledge of the pharmacokinetics of ethanol often give an expectation to non-scientists and courtroom advocates that many other drugs can be analysed and their levels predicted with a similar degree of certainty. Unfortunately alcohol is the exception rather than the rule and virtually no other drug analyses can be subject to the same sophistication in interpretation.

In the case of cannabis, most forensic toxicological interpretation involves either the blood concentration of the primary psychoactive ingredient, delta-9-tetrahydrocannabinol (THC) or the urinary concentration of its principal metabolite, 11-nor-delta-9-THC carboxylic acid (THC-COOH). THC is highly lipid soluble and is most commonly taken into the body by smoking, although it can also be orally ingested. THC absorbed through the lungs enters the circulation and is rapidly redistributed into lipid containing tissues including fat, brain and muscle [1]. The pharmacokinetic behaviour of THC in blood has been studied extensively, mostly using single controlled doses of cannabis. Concentrations initially rise rapidly after smoking and peak within an hour or less before a rapid fall as THC is redistributed, until a baseline is reached reflecting equilibrium between blood and saturation of lipid-containing tissue. While there is no formal definition of when the rapid redistribution phase ends and the baseline period begins, it is usually taken to be some hours after the last use of the drug. The baseline level may persist for days as the elimination kinetics of THC are much slower than for redistribution [2]. The amount of THC detected in whole blood, serum or plasma will depend on the total body load of THC and may also be affected by the amount of body fat. The long elimination half-life of THC means that baseline level of THC represents saturation of the body tissues (particularly the fatty tissues) with THC. The baseline level appears to be independent of body mass index [3,4].

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Our understanding of THC pharmacokinetics was originally derived from analysis of biological specimens from volunteers who smoked marijuana cigarettes under controlled conditions [2]. These studies resulted in the familiar curve that models the rise and fall of blood THC to baseline levels less than 5 ng/mL approximately 2–3 h after smoking. While widely accepted, the results of laboratory studies using controlled doses are based on conditions that are different from real world cannabis users. Attempts to derive mathematical models of THC concentration in body fluids as a function of time after use or, conversely, the estimation of time of use from body fluid levels of various cannabis related substances have met with some success in controlled dosing experiments where several analytes could be measured simultaneously [5,6]. Unfortunately this has not been possible in the common forensic scenario where time of use, extent of past use (regular vs. occasional) and impairment effects are unclear. THC levels have also been found to not decrease monotonically during abstinence, i.e. levels can rise and fall while maintaining a downward trend [7].

In court proceedings involving interpretation of cannabis toxicology, much weight has been put on opinions as to what defines a baseline concentration and whether it can be used to differentiate recent from past use of the drug. In recent years, cases have emerged that suggest that some heavy chronic users can achieve baseline concentrations of THC in blood much greater than would be expected from previous studies. It is also possible that the redistribution phase in these subjects is longer than in lighter recreational users, possibly due to greater saturation of body tissues with THC. In addition, there is some reason to believe that amounts of THC in cannabis preparations have been increasing in recent years [8–10], and that this may have a bearing on the baseline levels seen in heavy cannabis users. Unpublished data from the Victorian Institute of Forensic Medicine (VIFM) recently identified a level of 20 ng/mL of THC in whole blood in a heavy cannabis user 6 h after a traffic crash, after having been under medical observation and ambulance transport during that time. Such cases, coupled with significant gaps in the existing literature, highlight the need for a rigorous study of residual blood THC concentrations in heavy cannabis users, particularly as the formulation of forensic opinions regarding timing of cannabis use and its effects rely greatly on existing scientific evidence. We sought to address this gap in the literature by measuring residual THC concentrations in blood and oral fluid (saliva) and THC-COOH concentrations in urine, respectively, over seven consecutive days in a sample of cannabis users seeking residential detoxification. Our null hypothesis was that blood THC levels in newly abstinent heavy regular THC users would not differ from the accepted pattern of a baseline level less than 5 ng/mL within a few hours of the last reported use, with a steady monotonic decline over the 7 days of the study.

2. Experimental

2.1. Residential drug treatment unit model

Subjects were recruited from two community residential drug treatment units in metropolitan Melbourne, Australia. These 12-bed adult community based services provide medical treatment of low to medium complexity substance use disorders including withdrawal management and induction into recovery programmes. Multiple concurrent substance use is common: alcohol, tobacco and cannabis are the most common drugs used (although admissions for tobacco use alone are rare). The usual length of stay in the units is 7–10 days. Symptomatic and maintenance medication is prescribed by a staff medical officer following detailed assessment, and patients are monitored by nursing staff during admission. Activities on the unit include light physical exercise such as walking, exercise in a gymnasium and swimming. Massage, acupuncture or similar physical non-medical symptomatic therapies are offered where available, although availability and uptake of such options is variable and voluntary.

2.2. Subject selection

Subjects were included in the study if they had a history of regular cannabis use with cannabis dependence for at least 3 months up to the date of entry into the detoxification unit. Eligibility was assessed from answers to a questionnaire administered by one of the investigators. Subjects were asked about their medical and psychiatric history, drug use history, current medications, frequency and extent of cannabis use and the time of their last use of the drug. Subjects were excluded if they had a history of a documented substance induced psychosis within the last 2 years with continuing problems that may have affected cognition or the capacity to consent; long-term treatment with drugs that are taken outside medically recommended regimens and/or result in significant sedation with an effect on cognition or capacity to consent; active evidence, or significant risk of, a complex and severe acute withdrawal syndrome related to cessation of, or intoxication with, cannabis or other drugs, including features of; acute severe mood symptoms with risk of self-harm; aversion to or difficulties in blood sampling and remission of cannabis use prior to admission. Psychiatric conditions including depression, mood disorders or psychoses that were asymptomatic and well controlled on medication did not exclude subjects from participation in the study.

After having the procedure explained and giving informed written consent, subjects provided blood, urine and oral fluid (saliva) daily for one week (7 days).

2.3. Ethics approval

This study was approved by human research ethics committees at the VIFM (Ref No. EC 1/2012), Southern Health Melbourne (11304A) and Eastern Health Melbourne (E20/1112).

2.4. Specimen collection

Whole blood (up to 10 mL) was collected using a needle and syringe by facility medical nurses and stored immediately in polypropylene tubes containing 1% sodium fluoride/potassium oxalate (Sarstedt, Melbourne, Australia). At least 20 mL of urine was collected into a sterile container and 1 mL oral fluid was collected using Quantisal™ Oral Fluid Collection Device and diluted in 3 mL of buffer (Alere, Brisbane, Australia).

Following collection from a subject all samples were stored at 4 °C and promptly transported to the laboratory. Upon delivery to the laboratory these specimens were then stored frozen (−20 °C) until analysis. All samples were bar-coded and de-identified throughout the storage and analysis process. These samples were analysed within 1 month of collection.

2.5. Determination of THC and metabolites in whole blood, urine and oral fluid

2.5.1. Determination of THC in whole blood

A fully-validated method using international guidelines [11] for the determination of THC in whole blood was conducted on specimens collected in this study, using a Shimadzu Prominence LC-20AD HPLC system interfaced with an AB SCIEX Q-Trap® 5500 LC-MS/MS via an electrospray ionisation (ESI) source, and operated in multiple reaction mode (MRM) mode. The limit of detection for THC was 0.5 ng/mL. The limit of quantitation for THC in blood was