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Short communication

Δ^9-Tetrahydrocannabivarin testing may not have the sensitivity to detect marijuana use among individuals ingesting dronabinol

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ABSTRACT

The purpose of this study was to determine whether Δ^9-tetrahydrocannabivarin (THCV), a plant cannabinoid, is a sensitive measure to detect recent marijuana use in cannabis dependent patients. It has been purported that smoking an illicit plant cannabis product will result in a positive THCV urinalysis, whereas the oral ingestion of therapeutic THC such as dronabinol will result in a negative THCV urinalysis, allowing for discrimination between pharmaceutical THC products and illicit marijuana products. In a double-blind placebo-controlled trial to determine the efficacy of dronabinol in cannabis dependence, all 117 patients produced a positive urine for the marijuana metabolite 11-nor-Δ^9-THC-9-carboxylic acid; THC-COOH, but 50% had an undetectable (<1 ng/ml) THCV-COOH test. This suggests that THCV may not be a sensitive enough measure to detect recent marijuana use in all heavy marijuana users or that its absence may not discriminate between illicit marijuana use and oral ingestion of THC products such as dronabinol. We propose that the lack of THCV detection may be due to the variability of available cannabis strains smoked by marijuana users in community settings.

1. Introduction

Cannabis dependence is a serious condition that results in substantial occupational, medical, and psychiatric morbidity (D'Souza et al., 2004; Stinson et al., 2006). The primary active ingredient in marijuana, Δ^9-tetrahydrocannabinol (THC), has been associated with dose-dependent cognitive and motor impairment (Hunault et al., 2008; Weinstein et al., 2008). Large airway function impairment resulting in airflow obstruction and hyperinflation (Aldington et al., 2007), and neuropsychological deficits (Pope et al., 2001) have also been associated with smoked marijuana. While recent epidemiologic surveys suggest that lifetime and past month use have decreased among both adolescents and adults (Monitoring the Future (MTF), 2008; National Survey on Drug Use and Health (NSDUH), 2007) the overall prevalence of cannabis dependence has not changed substantially (Compton et al., 2004). Consistent with this, treatment admissions for cannabis dependence have increased by over 150% in the past fifteen years, with approximately 16% of all treatment admissions reporting marijuana as their primary drug of abuse Treatment Episode Data Set (TEDS), 2006.

Although there have been numerous studies assessing the efficacy of various psychosocial interventions for cannabis dependence (Budney et al., 2006; Dennis et al., 2004; Marijuana Treatment Project Research Group, 2004; Nordstrom and Levin, 2007), there have only been a handful of outpatient pharmacotherapy trials (Carpenter et al., 2009; Levin et al., 2004; Tirado et al., 2008). Most of the pharmacologic studies conducted have been laboratory studies utilizing nontreatment-seeking cannabis users (Hart, 2005), limiting the generalizability of these findings to the outpatient treatment-seeking cannabis dependent population. To date, the medication that has shown the most promise is dronabinol, the international non-proprietary name for a pure isomer of THC, which is also a naturally occurring component of cannabis considered to be responsible for its main psychoactive effects. Several studies suggest that dronabinol may mitigate cannabis withdrawal symptoms and reduce the subjective effects of smoked marijuana (Budney et al., 2007; Haney et al., 2004; Hart et al., 2002), although it did not reduce self-administration of smoked marijuana in one laboratory study (Hart et al., 2002). Furthermore, a recent laboratory study suggests that combining dronabinol with lofexidine, an alpha-2-adrenergic receptor agonist approved in the United Kingdom to treat symptoms of opiate withdrawal, might be superior to dronabinol alone as a treatment for marijuana withdrawal and relapse (Haney et al., 2008).

Given that dronabinol pharmacotherapy might be a clinically useful approach to reduce cannabis withdrawal symptoms and

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facilitate abstinence initiation and maintenance, investigation of this medication for treatment of cannabis dependence is underway. However, since ingestion of dronabinol produces a positive urine toxicology result for the THC metabolite, an objective method of distinguishing between smoked marijuana and oral THC administration would be clinically useful. One touted method has been to test for Δ^9-tetrahydrocannabivarin (THCV), a naturally occurring cannabinoid that is found in various strains of marijuana but is not present in orally administered THC products (Elsohly and Slade, 2005; Merkus, 1971; Shoyama et al., 1981). ElSohly et al. (1999) suggested that it might serve as a useful marker to distinguish the ingestion of cannabis from dronabinol. One study found that when four non-chronic marijuana users smoked one marijuana cigarette, THCV-COOH could be detected in the urine for up to two weeks. When these same participants were given dronabinol, THCV-COOH was not present (ElSohly et al., 2001), suggesting that THCV-COOH detection could be utilized as a method to distinguish recent illicit marijuana use from therapeutic dronabinol ingestion in outpatient double-blind placebo-controlled randomized trials for dronabinol treatment of cannabis dependence. Here we report on the sensitivity of THCV in urine samples collected prior to study entry in the detection of heavy marijuana use in treatment-seeking cannabis dependent outpatients.

2. Methods

2.1. Assessments

One hundred and seventeen patients who enrolled in a double-blind placebo-controlled trial to assess the efficacy of dronabinol for the treatment of cannabis dependence were required to provide a urine sample prior to study entry. If the patient reported that he or she had used marijuana at least five times in the past week and if the urine sample was positive for the metabolite 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), the patient was entered into the study. All urine samples were tested for 11-nor-Δ^9-tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH). In addition, all urine samples were also tested for creatinine. As these patients had not yet received any medication, it was possible to compare THCV-COOH urine results with quantitative THC-COOH urine levels without the confounding variable of dronabinol ingestion.

All laboratory testing was conducted at the Analytical Psychopharmacology Laboratory of the Nathan Kline Institute. THCV-COOH and THC-COOH concentrations were determined by gas chromatography–mass spectroscopy (GC–MS), operated in a negative chemical ionization (NCI) mode and using their deuterated derivatives as internal standards. A 15 m Rtx-5 Amine capillary column was programmed from 80 °C (holding for 1 min) to 280 °C at increasing rate of 30 °C/min. The target compounds and the internals were extracted with hexane-ethyl acetate (9:1) at pH 10, and derivatized with trifluoroacetic anhydride and trifluoroethanol. The standard curves encompassed the range of 1–1000 ng/ml for both THCV-COOH and THC-COOH with the limit of quantification set at 1 ng/ml. The coefficients of variation of inter- and intra-days for both target compounds were <7%.

2.2. Data analysis

The sensitivity of THCV-COOH in the detection of marijuana use was determined by calculating True Positive (number of samples with THCV-COOH detected)/True Positive (number of samples THCV-COOH detected) + False Negative (number of samples with no THCV-COOH detected). Looking at the sub-sample who had detectable THCV-COOH levels, the correlation between THC-COOH concentration and THCV-COOH concentration was determined using a Pearson's correlation. Secondary analysis was conducted using a linear regression model.

3. Results

Sample demographics are provided in Table 1. Every baseline sample ($n = 117$) was positive for THC-COOH. The mean THC-COOH concentration was 1724 ng/ml (±2553). Conversely, only 50% ($n = 58$) of the samples had a detectable THCV-COOH level. The sensitivity for THCV-COOH was .496. For the samples that were detectable (≥1 ng/ml), the mean THCV-COOH level was 4.40 ng/ml (±3.87). Individuals with a detectable THCV-COOH level had a mean THC-COOH of 2705 ng/ml (±3281) compared to the undetectable sample ($n = 59$) that had a mean THC-COOH of 760 ng/ml (±743). There was a significant correlation between THC-COOH and THCV-COOH levels ($r = .446$, $p < .01$). The linear regression was also significant ($\beta = .446$, $t = 4.98$, $p = .000$). With every 1000 ng/ml increase in THC-COOH there is an associated increase in the THCV-COOH by 1 ng/ml. Fig. 1 provides a scatter plot of these data.

Table 1
Baseline demographics.

	$n = 117$
Demographics	
Age (years)	38.7 ± 10.4
Male	96 (82%)
Race	
African-American	25 (21%)
Hispanic	25 (21%)
Caucasian	63 (54%)
Asian	3 (3%)
Other	1 (1%)
Education (years)	14.4 ± 2.6
Pattern of marijuana use	
Age 1st use (years)	15.2 ± 3.0
Age of regular use (years)	18.4 ± 5.0
Days used (per week)	6.6 ± 0.9
Amount used (joints per using day)	5.4 ± 8.0

4. Discussion

Based on previously published reports (ElSohly et al., 1999, 2001; Elsohly and Slade, 2005), this study was designed so that GC–MS testing for THCV could be assessed for its ability to reliable detect illicit marijuana use in cannabis dependent outpatients. Because eligibility criteria required participants to have smoked marijuana at least five times in the week prior to study entry as part of a pattern of chronic cannabis dependence, we had the opportunity to assess the sensitivity of THCV to detect recent marijuana use in individuals who are regularly smoking "street" marijuana. Although there was a significant correlation between THC and THCV levels, THCV testing alone is not sensitive enough to detect all recent marijuana use.

There are several explanations as to why the results of this study differ from those of previously published laboratory studies. THCV concentration varies considerably among different cannabis strains

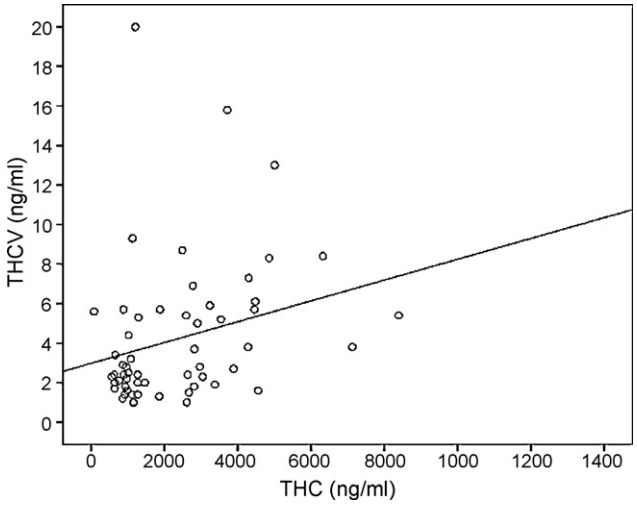

Fig. 1. Association between THCV-COOH levels and THC-COOH levels in marijuana using treatment seekers ($n = 58$; $r = .446$, $p < .01$). *Note:* there was an outlier (THC-COOH = 23, 380 ng/ml) that was included in the analysis but was excluded from the graph because of scale reduction.