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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 THC urinalysis, whereas the oral ingestion of therapeutic THC such as dronabinol will result in a negative THC 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.

Keywords

urinalysis; cannabis; dronabinol

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

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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), 2009) 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; Marihnana 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 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). El Sohly 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 -tetrahydrocannabinol-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 pH10, 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 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 ($\pm$ 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 ($\geq$ 1 ng/ml), the mean THCV-COOH level was 4.40 ng/ml ($\pm$ 3.87). Individuals with a detectable THCV-COOH level had a mean THC-COOH of 2705 ng/ml ($\pm$ 3281) compared to the undetectable sample (n=59) that had a mean THC-COOH of 760 ng/ml ($\pm$ 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 1,000 ng/ml increase in THC-COOH there is an associated increase in the THCV-COOH by 1 ng/ml. Figure 1 provides a scatter plot of these data.

4. Discussion

Based on previously published reports (ElSohly et al 1999; ElSohly et al 2001; Elsohly and Slade 2005), this study was designed so that GC-MS testing for THCV could be assessed for its ability to reliably 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 and in some naturally occurring strains may be entirely absent (Hillig and Mahlberg 2004; Small and Beckstead 1973). A related phenomenon has been described with THC content, which can vary considerably depending on a multitude of factors, such as the cultivated cannabis strain, location, climate, and light exposure of the harvested plant, and how much time has elapsed since the product was initially harvested (Licata et al 2005; Sifaneck et al 2007). Such factors may also affect the subjective quality of the drug (Chait and Pierri 1989). While THCV analysis of domestically available marijuana grown or seized in the United States is not available, it is likely that THCV content of the marijuana smoked by patients in New York City varies. Hillig and Mahlberg (2004) characterized quantitative and qualitative patterns of cannabinoid variations in various cannabis strains and found substantially higher levels of cannabidivarin (CBDV), either in the presence or absence of THCV, in *Cannabis Indica* compared to *Cannabis Sativa*.

Pertwee et al. (2008) reported that in studies with mice, Δ^9 -THCV acted as a CB₁ receptor antagonist at low doses and a CB₁ receptor agonist at high doses. However, the relationship of the THCV doses studied to typical serum levels achieved by consuming cannabis available in the community is unknown. Therefore, while the available evidence suggests that THCV has potent interactions at the CB₁ receptor its contribution to the psychoactive properties of cannabis are still not clearly understood. Hillig and Mahlberg (2004) observed that THCV was not present in many cannabis strains world-wide and posited a theory that humans may have selected against THCV in cannabis cultivation based on its cannabinoid receptor effects. The results reported in this study are consistent with those reported by Hillig and Mahlberg (2004); THCV is not present in a substantial proportion of cannabis available in the community. Further research is needed to better understand the role of THCV in producing cannabis-induced psychoactive effects, particularly whether its presence enhances or diminishes desirable subjective effects.

Since all published laboratory studies of THCV testing have used NIDA-grown marijuana and since all published data using NIDA marijuana have affirmed the presence of THCV, it is unquestionable that THCV is present in this strain. However, as suggested by the results of the present study, there may be substantial variability in the THCV content in cannabis cultivated and sold in the community and some domestically grown cannabis may contain minimal or no THCV at all. At present, it does not appear that THCV can be used as a reliable detection method of recent marijuana use since a negative test is not conclusive that there was no marijuana use. Nor can it be used as a reliable discriminatory method between illicitly smoked cannabis and therapeutic dronabinol ingestion. A corollary to this finding is that since there may be variability between NIDA-grown marijuana and marijuana available in the community, generalizing the results of laboratory research findings using NIDA-grown marijuana to the general population may have limitations.

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Figure 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

Table 1

Baseline Demographics

	N=117
<i>Demographics</i>	
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
<i>Pattern of Marijuana Use</i>	
Age 1 st 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