Medical and Recreational Use of Marijuana: Have We Missed the Boat Again?

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Just as some state governments (like Massachusetts) have moved to decriminalize the possession of personal amounts of marijuana (1 ounce or less), and license "dispensaries" to sell marijuana for legitimate medical purposes, or allow the non-medical use of marijuana for recreational purposes (e. g., Colorado), the wisdom of these decisions has been questioned following reports of two deaths associated with the oral ingestion of marijuana-laced cookies or candy.[1]

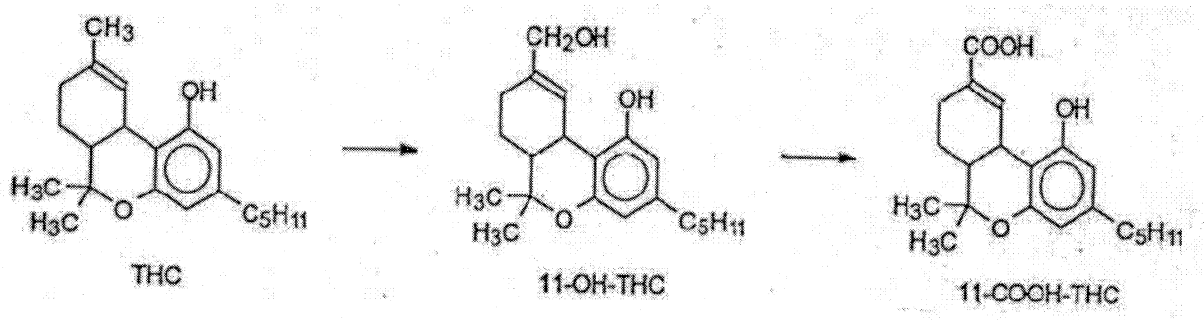
Case 1 involved a 19-year-old college student from Wyoming named Levi Thomba Pongi. According to the USA Today article, witnesses say that Mr. Pongi ate a marijuana-laced cookie and shortly thereafter began rambling incoherently. A little while later Mr. Pongi jumped to his death from the balcony of a Denver hotel. Mr. Pongi was reported to have had a blood THC concentration of 7.2 ng/mL, a concentration that would be found approximately 2 hours after smoking a 3.55% THC marijuana cigarette, and the Denver coroner listed marijuana intoxication as a significant factor in his death. One should remember that plasma THC concentrations are approximately twice those of whole blood, and due to the great variability in metabolism and distribution in the population, reliable correlations between blood or plasma concentrations and time of smoking cannot be reliably established.

The second case involved Richard Kirk of Denver, CO, who developed hallucinations and rambling speech after eating marijuana-containing candy and taking prescription medication at the same time. The prescription medication was not named. In the midst of Mr. Kirk's apparent psychotic break he fatally shot his wife while she was on a 911 call asking for urgent help because her husband was "totally hallucinating" and scaring the kids. Mr. Kirk now faces first-degree murder charges stemming from that fatal shooting. The USA Today article offers opinions from a psychologist, a psychiatrist, a legislator and a marijuana advocate on how the oral ingestion of THC induced psychosis, suicidal acts and violence not generally seen following the smoking of marijuana. However, none of those who commented were pharmacologists, or had advanced training in pharmacokinetics.

There is substantial pharmacology literature on the differences between smoking marijuana and ingesting it. Tetrahydrocannabinol (THC), shown in Figure 1, normally undergoes oxidation of the 11 CH_3 group to the 11-OH-THC metabolite, CH_2OH, by the polymorphic CYP2C9.[2] The 11-OH-THC metabolite is psychoactive, and is finally oxidized to the inactive, 11-nor-9-carboxy-THC (THC-COOH) acid which appears in the blood and urine.[3] When THC is smoked in the traditional ways, smoking of a single marijuana cigarette containing either 1.75% or 3.55% THC produced peak plasma levels of 11-OH-THC of 6.7-7.5 ng/mL which were measurable in the low dose group for 4.5 hrs and 11.2 hrs in the high dose group.[4]

The psychotropic effects of the 11-OH-THC metabolite were demonstrated by Lemberger in 1973, when he administered tritiated IV doses of THC, 11-OH-THC (formulated in ethanol) or ethanol, under blinded conditions, to nine casual marijuana users.[6] Following

Figure 1



THC; tetrahydrocannabinol

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the administration of 1 mg of 11-OH-THC, a marked tachycardia and euphoric "high" occurred in 3-5 minutes, and psychologic effects correlated well with 11-OH-THC plasma levels. However, IV administration of 1 mg of THC required a latency period of 10-20 minutes after IV administration before the peak subjective "high" was reported by the subjects. Lemberger et al interpreted these results to indicate that the psychologic effects of THC were at least partially mediated through the 11-OH-THC metabolite and the latency period was indicative of the time required to convert the THC to 11-OH-THC.

Although we do not have any information on the genotype of CYP2C9 or capacity of the two victims to metabolize THC, Lemberger's study indicates that the genetic polymorphism known to be present with the CYP2C9 enzyme could significantly impact the effect of oral marijuana ingestion on the development of CNS toxicity and the probability of precipitating a psychotic reaction in fast metabolizers who rapidly produce large amounts of 11-OH-THC following oral ingestion of cookies and candy containing marijuana. The CYP2C9 exists as three genotypes, CYP2C9*1/*1, CYP2C9*2/*2, and CYP2C9*3/*3, which can be homozygous or heterozygous (e.g., CYP2C9*1/*3).[2] Studies indicate that the *1/*1 homozygous genotype is the most active enzyme and the *3/*3 the least active, with other heterozygous combinations somewhat interim. Subjects with the *1/*1 homozygous genotype had a shorter mean terminal elimination rate for THC (7.5 hrs) in comparison to the *3/*3 genotype (22.1 hrs), and more *3 alleles carried by a subject, the greater the sedation experienced.[2]

Both the case reports and the study by Lemberger also demonstrate how a change in the route of administration of a drug can turn a substance like marijuana, which Sanjay Gupta, MD on CNN, called a rather innocuous substance, into a dangerous psychoactive substance capable of causing psychotic episodes and precipitating great danger in the population at large. Another important lesson to be gleaned from these case reports is the apparent inadequate attention paid to the administration of marijuana by the oral route. Most of the published pharmacologic and epidemiologic studies on marijuana during the past few decades have focused on the smoking of marijuana, and relatively few publications have studied the metabolism and pharmacologic effects of marijuana by the oral route. The appearance of 11-OH-THC in the blood after smoking marijuana has been reported in several publications [3,4] although the 11-OH-THC is often less than 20% of the parent compound following smoking, while ingestion can produce 11-OH-THC blood levels comparable to THC, the parent compound.[5] Jokes about "marijuana brownies" have been made for decades, but it is apparent that differences in the route of administration of marijuana lead to a very different constellation of effects which dramatically change from mild to moderate euphoria by the inhalation route to severe CNS toxicity by the oral route.

Lemberger's study is 40 years old, but current investigators in the marijuana field have failed to look for toxic effects of marijuana when administered by the oral route. It is now apparent that oral administration of marijuana to a subject predisposes them to the possibility of a severe psychotic reaction. Those who produce a large amount of 11-OH-THC, due to a high level of CYP2C9 activity, are at the greatest risk. Since there is currently no way to routinely phenotype potential users and determine a level of risk prior to ingestion of marijuana, a critical public health issue exists. Therefore, those who wish to use marijuana should choose to smoke it, rather than eat it, in order to avoid the risk of a serious CNS adverse effect. While inhaling hot smoke certainly is not a healthy practice, the inhalation route appears to present less risk of a serious adverse psychiatric reaction, and the dose can be titrated by the user far more easily than the oral route.

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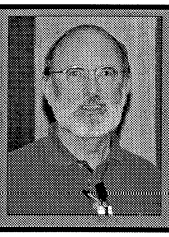

CASE NOTES

Send interesting *"Case Notes"* to Section Editor

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Case Report of a Fatality Involving a New Designer Drug: N-(2-methoxybenzyl) 2,5-dimethoxy-4-bromophenethylamine (25B-NBOMe)

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Introduction

N-(2-methoxybenzyl)2,5-dimethoxy-4-bromophenethylamine (25B-NBOMe), see Figure 1, is a derivative of the phenethylamine hallucinogen 2C-B.[1] It acts as a potent partial agonist for the serotonin $5HT_{2A}$ and $5\text{-}HT_{2C}$ receptors and appears to have stimulant and hallucinogenic effects on users.[1-3] It has been seen with LSD that the stimulation of the $5\text{-}HT_{2A}$ receptors appears to be essential for the hallucinogenic effects of the drugs.[1] This may account for the powerful psychedelic effects experienced at very low doses of the NBOMes.[2]

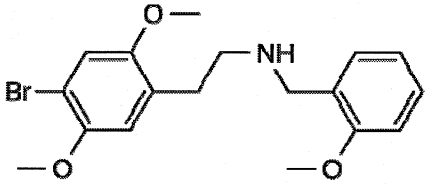

Figure 1: Chemical Structure of 25B-NBOMe

Unlike LSD, however, the NBOMes have significant sympathomimetic effects and can lead to acute toxicity, in addition to the behavioral hazards associated with LSD use.[2] Anecdotal reports indicate that the powder in doses of 50-250 µg may be administered sublingually by insufflation or applied to the buccal cavity. Blotter paper, the preferred choice of users (see Figure 2), usually contains higher doses ranging from 500-800 µg.[4] Based on user reports (EROWID), initial effects are felt within 15 minutes with a duration of up to 12 hours.[1,3] Individuals presenting to the emergency departments with acute NBOMe toxicity might experience cardiovascular complications, agitation, seizures, hyperthermia, metabolic acidosis, organ failure and death.[2]

Case History

An eighteen year old Caucasian female was at home with three friends and bought what they thought was LSD. Three individuals took the "LSD" which was on blotter paper. One individual took one blotter paper and the other two, including the deceased, took