Straight Tox

Medical Marijuana – More Than Blowing Smoke?

by Dwain Fuller, BS, D-FTCB, TC-NRCC

This headline recently caught my eye: "Dying Woman Loses Marijuana Appeal". This Associated Press article tells the story of Angel Raich who lost her appeal with the 9th U.S. Circuit Court of Appeals to be allowed to legally use marijuana under what is called the "right to life theory"; the principle that the gravely ill have the right to marijuana to keep them alive when legal drugs fail.

The legalization of marijuana is an issue fraught with political drama. The debate ranges from factions that would have marijuana simply made legal as a grow-your-own commodity for self-medication or recreation to those who advocate it or its chemical constituents as a well-controlled legally-prescribable medicine. If you are like me, you have sometimes wondered what all the fuss is about. In this article I hope to shed some light on some questions that many of us have wondered about, such as: **If THC is available by prescription for oral use, as it has been for years, why is there such a push to try to legalize marijuana itself? Do other cannabinoids beside THC have scientifically-validated medical uses? Why the insistence on smoking marijuana?**

The first person that came to mind to help answer these questions was Dr. Marilyn Huestis. It would take more space than is allotted to this column to list Dr. Huestis' qualifications in this field, but for those few who do not know her, she is Chief of the Chemistry and Drug Metabolism Section of the National Institute on Drug Abuse, and suffice it to say, one of the world's leading experts on cannabinoids. So it is to her that I offer many thanks in pointing me in the right direction and giving me more information on cannabis than I could possibly write down.

First a little history: The first verifiable use of cannabis in medicine goes back to at least 2000 BC Egypt where it was used to treat sore eyes. Through the ages, however, it has been used to treat the pain of childbirth, earache, hemorrhoids, and rheumatism, as well as edema, inflammation, asthma, tetanus, hydrophobia, delirium tremens, infantile convulsions, neuralgia, cholera, and much more. Today, THC in its legal compounding as Marinol®, is used as an antiemetic for chemotherapy patients and as an appetite stimulator for those with HIV-

associated wasting syndrome. However, proponents of legalization of marijuana argue that marijuana is, or may be, effective in treating multiple sclerosis, cancer, AIDS, glaucoma, depression, epilepsy, migraine, asthma, pruritis, sclerodoma, severe pain, and dystonia.

The study of the pharmacology of cannabinoids has been ongoing for many years, but it is only in the last twenty years have we begun to characterize the endogenous cannabinoid system. There are at least two types of cannabinoid receptors, CB1 and CB2. CB1 receptors are widely distributed and are abundant in areas of the brain that are concerned with movement and postural control, pain and sensory perception, memory, cognition, emotion, autonomic and endocrine functions. CB2 receptors are less well understood, but exist in the immune tissues and are believed to be involved in the immunological effects of cannabinoids. This along with the discovery of the endogenous ligand, anandamide, which acts as a partial agonist at the CB1 receptor, as does THC, has provided new insights into a neuromodulatory scheme that may provide new treatments for painful disorders.

So what are the scientific facts of this debate? The two main issues as far as the science goes have to do with the possible efficacy of other cannabinoids in addition to THC and the inter-related issues of route of administration, absorption, distribution, and bioavailability.

Marinol®, the currently available prescription form of THC, is synthetically produced and contains only the THC cannabinoid. However, there are more than 60 known cannabinoids contained in the cannabis plant, such as cannabidiol, cannabinol, cannabichromene, and cannabigerol. Many of these have pharmacological activity: psychoactive, antiemetic, analgesic, and anti-inflammatory. Furthermore, some cannabinoids may simply modify the pharmacology of the others. As a result of focusing on only the THC cannabinoid, we may be missing out on many useful cannabinoids that are produced by the cannabis plant. Thus, the emphasis on plant-derived cannabinoid preparations.

Secondly, as toxicologists know, route of administration can have a profound effect on the peak plasma concentration of a drug. In one National Institute on Drug Abuse (NIDA) study in six volunteers, each of whom smoked cigarettes containing 15.8 mg and 33.8 mg of THC, peak plasma THC concentrations occurred within 5 to 10 minutes after smoking began with mean peak concentrations of 84 ng/mL and 162 ng/mL, respectively. In contrast, THC has a low oral bioavailability. Although Marinol's manufacturer reports that 90% to 95% of the THC is absorbed, due to first-pass metabolism and high lipid solubility only about 10% of the dose reaches systemic circulation. Peak plasma concentrations of THC from the ingestion of Marinol range from 1.3 ng/mL to 7.9 ng/mL with the time to peak plasma concentration ranging from 1 to 2.5 hours. Furthermore, chemotherapy patients who are suffering from nausea may not be able to retain an oral dose long enough to achieve an efficacious concentration.

In early 2006 a product known as Sativex®, an oromucosal spray developed by the UK company GW Pharmaceuticals, was given permission from the United States Food and Drug Administration to enter into Phase III trials in the U.S. This product hopes to address both the issues of additional useful cannabinoids as well as route of administration issues. Sativex® is a cannabinoid compounding derived from the precisely controlled cultivation of marijuana. It contains both THC, the principle psychoactive ingredient in marijuana as well as cannabidiol (CBD) which is not psychoactive and is purported to be almost completely absent from most of the cannabis grown in North America. Both THC and CBD have important pharmacology: THC has analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant and anti-emetic properties, while CBD has anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective, and immunomodulatory effects. CBD is not intoxicating and it has been postulated that the presence of CBD in cannabis may alleviate some of the potentially unwanted side-effects of THC. GW Pharmaceuticals believes that the beneficial therapeutic effects of cannabis based medicines result from the interaction of different cannabinoids.

Each spray of Sativex® reproducibly delivers a dose of 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa where it is absorbed, thereby avoiding first-pass metabolism in the liver. Although concentrations of both THC and CBD are generally less than 10 ng/mL after the administration of about 10 mg each in Sativex, onset of action is typically 15 – 40 minutes, which allows the patient to titrate the dose according to symptoms. Time to peak plasma concentration (Tmax) is generally 2 – 4 hours.

At this time clinical trials with THC and CBD are ongoing. These involve the pharmacokinetics of sublingual and buccal mucosa absorbed cannabinoids, the effects of THC and CBD on sleep, the efficacy of these cannabinoids for the relief of neuropathic pain and other symptoms associated with Multiple Sclerosis, as well as chronic pain. In April 2005 Sativex® received regulatory approval in Canada for the symptomatic relief of neuropathic pain in adults with Multiple Sclerosis.

It appears that the pharmaceutical industry and the government are in the process of allowing science to decide the issues of the medical marijuana debate, as it should be. As for toxicologists, we may soon have to solve the emergent issue of how to tell legitimate cannabinoid use from clandestine. Cannabidiol assays anyone?

Thanks again to Dr. Marilyn Huestis for her invaluable contributions to this article.

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DWAIN C. FULLER, D-FTCB, TC-NRCC
FORENSIC TOXICOLOGY CONSULTANT

817-319-5501

DWAIN@FORENSICTOXICOLOGYCONSULTANT.COM

WWW.FORENSICTOXICOLOGYCONSULTANT.COM