THERAPEUTIC DRUG MANAGEMENT AND TOXICOLOGY DIVISION NEWS
AACC Better health through laboratory medicine.
Volume 4 | Issue 1 |February 2018

Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

In This Issue:

Mescaline, a Schedule I drug with a special exemption

Peter L. Platteborze, PhD, DABCC, FAACC; Jonathan Vela* & Milo Colton PhD, JD
St. Mary's University, San Antonio, TX (*part of senior thesis project)

Mescaline (3,4,5-trimethoxyphenethylamine) is a hallucinogenic phenethylamine alkaloid found in a several plant species endemic to the Americas, most notably peyote. Human ingestion can induce a psychedelic state that is reportedly comparable to LSD and psilocybin. Native Americans have used peyote for ritualistic and medicinal purposes dating back several millennia. This long established use has led to great contention between the United States (U.S.) government and many of its indigenous people. While mescaline is listed as a Schedule I drug by the U.S. Drug Enforcement Agency, the established historical use of peyote along with sustained political lobbying successfully led to its consumption being legally permitted as an entheogen by members of the Native American Church.

Plant sources: Mescaline is naturally synthesized by several members of the Cactaccea plant family to include the San Pedro cactus (*Echinopsis pachanoi*), the Peruvian torch cactus (*E. peruviana*) and most notably, peyote (*Lophophora williamsii*). The Echinopsis grow naturally in the Andes Mountains of South America. Mescaline is also found in very small amounts in certain members of the Fabaccea (bean) family. Of these plants, peyote contains the greatest mescaline content.

Peyote is a small spineless cactus that grows in arid regions of Northern Mexico & Southern Texas (Figure 1). The above ground cactus crown consists of multiple disc-shaped

buttons that contain the highest level of mescaline and are the primary source of the drug. Overharvesting, expanding commercial development and its slow growth rate have led to listing peyote as an endangered species in Texas. It is usually found among desert scrub in the Chihuahuan Desert, especially where there is limestone. A wide range of phenethylamine alkaloids are produced in peyote; the principal one being mescaline. The mescaline content of freshly cut buttons is ~0.4% but when dried can be up to 6% (1).

It is hypothesized that mescaline is the end product of a plant stress response pathway that uses catecholamines, similar to how animals release cortisol. Mescaline is naturally biosynthesized from the amino acids tyrosine and phenylalanine. In *L. williamsii*, dopamine is enzymatically converted into mescaline via a hydroxylation and two methylations.

Figure 1. Left- The natural growth range of the peyote plant. Right- Peyote buttons.

History: Peyote has a long history of ritualistic and medicinal use by Native Americans. In 2005, research anthropologists digging at the Shumla Cave in Texas recovered two peyote buttons that were radiocarbon dated to between 3780 to 3660 BCE (2). These results suggest that indigenous people were likely to have consumed peyote (i.e. mescaline) for at least 5,600 years. Several other archeological sites have found related results dating from 1070 BCE to more recent times.

Native American Indians do not consider peyote to be a conventional drug and this mindset ultimately led to its designated special exemption. Apart from rituals, indigenous peoples have used it as a medicine for such diverse ailments as pain, fever, snakebites, rheumatism, cramps, hemorrhages, headaches, diabetes, blindness, and pulmonary diseases (3). From the first contact in the New World, Spanish explorers observed the Indian use of peyote and saw it as a threat to their governance. The Roman Catholic Church imposed the first ban that was later promulgated by the U.S. government. Despite these laws, native Indians continued their traditions in covert Tipi Ceremonies. Paradoxically, peyote use flourished when the government forced multiple tribes to be concentrated in reservations located in the American southwest. Discovery of this led to more rigorous enforcement to which the Indians countered its use had become both a holy medicine and a Christian sacrament (4). In 1918, the nationally accepted ban was lifted in Oklahoma when the Native American Church was incorporated. Church members were legally permitted to use sacramental peyote in their services, ceremonies and rituals. The following year mescaline was first synthesized. Throughout the remainder of the 20th century, various states and the federal government enacted legislation that banned or allowed peyote's use by the Church. A national standard was set in 1970, with the passing of the Controlled Substances Act which listed mescaline as a Schedule I hallucinogenic drug making peyote use illegal. Ultimately in the 1990s, after extensive lobbying, a new federal law was enacted that created a special exemption for the Native American Church and its members. Title 21, Part 1307.31 of the Code of Federal Regulations (CFR) states: The listing of peyote as a controlled substance in Schedule 1 does not apply to the nondrug use of peyote in bona fide religious ceremonies of the Native American Church, and members of the Native Church so using peyote are exempt from registration. Any person who manufactures peyote for or distributes peyote to the Native American Church, however, is required to obtain registration annually and to comply with all other requirements of law.

Administration and Dosage: Mescaline is related to the more potent synthetic amphetamine-derived street drugs 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), 2C-B, and p-

methoxyamphetamine. Its chemical structure is shown in Figure 2. Illicit mescaline use and religious abuse seems limited. In a 12-year retrospective study, there were only 31 cases reported to the California Poison Center (5). By far its most prominent use involves oral consumption during Native American religious rituals. Harvested peyote buttons are usually boiled in water to produce a psychoactive tea or they are chewed to release the mescaline. Only rarely have individuals been reported to swallow gelatin capsules containing powdered peyote buttons or to insufflate or smoke this powder (5). A single oral hallucinogenic dose of mescaline is estimated to range from 200 – 500 mg as the hydrochloride or sulfate salt and the effects can persist for up to 12 hrs. (1). Tolerance builds with repeated usage that lasts for a few days. Cross-tolerance may also exist with other serotonergic based psychedelics like LSD and psilocybin.

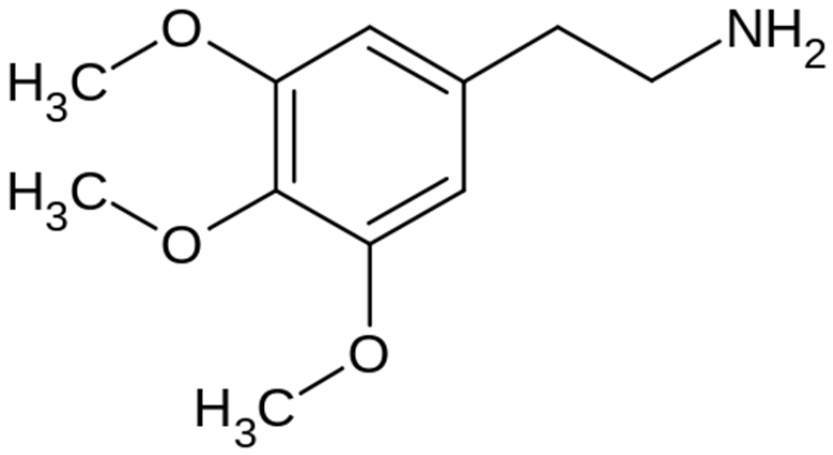

Figure 2. Chemical structure of Mescaline, $C_{11}H_{17}NO_3$.

Pharmacology: Peyote ingestion is reported to trigger states of profound insight that have been described as deeply transcendent or spiritual. Users may also experience a significantly altered sense of time and rich visual or auditory effects to include synesthesia. Peyote has an extremely bitter taste and many users become nauseated prior to the onset of psychoactive effects. Mescaline's hallucinogenic properties stem from its structural similarities to the neurotransmitters serotonin and dopamine. In animals, mescaline binds with high affinity and

activates the serotonin 5-hydroxytryptamine 2A receptors (5-HT2a). This is presumed to cause neuronal excitation in the brain's prefrontal cortex. Mescaline also binds and activates the serotonin 5-HT2C receptor.

Very few human experiments with mescaline have been conducted since the Controlled Substances Act was passed making it a Schedule I drug. Blood levels of total radioactivity in 12 healthy men given a 500 mg labeled oral dose of mescaline averaged 3.8 mg/L at 2 hrs. and 1.5 mg/L at 7 hrs. post-ingestion (6). It has an estimated half-life of 6 hr. When a 350 mg/70 kg intravenous dose was given to 11 healthy men, a peak concentration of 14.8 mg/L was observed at 15 min that declined to 4.9 mg/L by 1 hr and 2.1 mg/L by 2 hr (7).

Almost 90% of a labeled oral dose of mescaline is excreted in the 24 hr urine (6). From 55 – 60% of the primary excretion product is the unchanged drug. Excreted metabolites include 3,4,5-trimethoxyphenethylacetic acid (27 – 30%), N-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine (~5%), and minute amounts of N-acetylmescaline and 3,4,5-trimethoxybenzoic acid. All of these metabolites are presumed to be pharmacologically inactive (1). Limited research suggests mescaline is not metabolized by CYP2D6 but maybe metabolized by monoamine oxidase.

Human Toxicity: Common adverse effects post-ingestion include nausea, numbness, emesis, abdominal cramps, diarrhea, diaphoresis, tremor, anxiety, mydriasis, visual/ perceptual distortions & potentially disturbing hallucinations. The gastrointestinal effects can be severe and may persist for several days. Peyote is also known to cause potentially dangerous variations in heart rate, blood pressure and breathing. Based upon intraperitoneal experiments, the LD50 is estimated to be 212 mg/kg in mice, 132 mg/kg in rats and 328 mg/kg in guinea pigs.

A few fatalities related to peyote-mescaline use have been reported. One death was attributed to esophageal bleeding caused by forceful emesis post-ingestion in a Native American male with a history of chronic alcohol abuse (8). He had an ante mortem mescaline blood level of 0.48 mg/L and a urine level of 61 mg/L. Another man who was shot multiple times during a religious ceremony had a postmortem femoral blood mescaline level of 3.0 mg/L

and a liver level of 8.2 mg/kg (9). Last, there was an adult male who died of head injuries after bizarrely jumping from a 600-foot hill while under the influence of mescaline (10). He had a postmortem mescaline concentration of 9.7 mg/L in blood, 71 mg/kg in liver and 1,163 mg/L in urine. No other illicit drugs were found in any of these cases.

Peyote use does not seem to be associated with physical dependence. Recent research has found no evidence of long-term cognitive issues related to its chronic use amongst members of the Native American Church except for those with preexisting mental health issues. Flashbacks after religious use have not been reported. No antidote currently exists to treat overdosed patients. Supportive care may involve the administration of benzodiazepines for sedation and intravenous fluids.

Lab Analysis: Mescaline has been identified and quantified in several biological fluids by gas chromatography (GC) with nitrogen-selective detection or by liquid- or GC-mass spectrometry (1). Mescaline is stable in blood and urine for at least 30 days at room temperature, 4^{o} C or at -20^{o} C (11). Due to the drug's low prevalence, it is not conventionally tested in toxicology laboratories. However, several national reference labs can provide testing such as NMS, LabCorp and MedTox.

Conclusion: Despite mescaline being listed as a Schedule I drug, a special exemption in the CFR permits its use during religious ceremonies of the Native American Church. Consumption usually involves the legal oral ingestion of peyote buttons or peyote tea. Mescaline has mild hallucinogenic properties and consumption does not appear to cause physical dependence.

References:

1. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 9th Ed. 2011. Seal Beach, CA: Biomedical Publications. pp 1012-13.

2. El-Seedi HR, De Smet PA, Beck O, Possnert G, Bruhn JG. (2005). Prehistoric peyote use: alkaloid analysis and radiocarbon dating of archaeological specimens of Lophophora from Texas. *J Ethnopharmacol* 101: 238-42.

3. Labate CT, Cavnar C. Peyote: History, Tradition, Politics and Conservation. 2016. Santa Barbara, CA: Praeger Publications.

4. Smith H, Snake R. One Nation Under God: the Triumph of the Native American Church. 1996. Santa Fe, NM: Clear Light Publications.

5. Carstairs SD, Cantrell FL. (2010). Peyote and mescaline exposures: a 12-year review of a statewide poison center database. *Clinical Toxicology.* 48(4): 350-53.

6. Charalampous KD, Walker KE, Kinross-Wright J. (1966). Metabolic fate of mescaline in man. *Psychopharmacolgia.* 9: 48-63.

7. Mokasch LC, Stevenson I. (1959). The metabolism of mescaline with a note on correlations between metabolism and psychological effects. *J Nerv Ment Dis.* 129: 177-83.

8. Nolte KB, Zumwalt RE. (1999). Fatal peyote ingestion associated with Mallory-Weiss lacerations. *West J Med.* 170: 328.

9. Henry JL, Epley J, Rohrig TP. (2003). The analysis and distribution of mescaline in postmortem tissues. *J. Anal. Tox* 27: 381-82.

10. Reynolds PC, Jindrich EJ. (1985). A mescaline associated fatality. *J Anal Tox.* 9: 183-84.

11. http://www.nmslabs.com/test-catalog/mescaline@0. January 6, 2018.

THERAPEUTIC DRUG MANAGEMENT AND TOXICOLOGY DIVISION NEWS
AACC Better health through laboratory medicine.
Volume 4 | Issue 1 |February 2018

Editor's Corner: Division News

Dear Readers,
I recently heard from Manoj Tyagi, PhD, Medical Lab Director of Captiva Lab, that they are using alternate matrix (other than serum or urine: saliva or hair) for Drugs of Abuse testing. Could you please let us know how prevalent the practice is in our labs? And, please do not forget the Medical Lab Professionals Week, April 22-28, this year! Furthermore, let us welcome Jessica M. Boyd, PhD, as the newly appointed Scientific Program Task Force Chair of the Division. The Division awarded Young Investigator Award to Fred Strathmann, PhD, and Outstanding Abstract to Sarah Delaney ("Targeting Drug Transport: Using Vitamins to Inhibit Bcrp-Mediated Transport of Methotrexate into Milk") in 2017.

Pradip Datta, Editor.

AACC TDM TOX Web Resources:

https://www.aacc.org/community/divisions/tdm-and-toxicology/

Upcoming Conferences/Courses

CLINICAL TESTING USING MASS SPECTROMETRY: A HANDS-ON TRAINING COURSE; March 26, 2018 - March 30, 2018; in Emory University, Atlanta, GA. Registration link: http://cmetracker.net/EMORY/Login?FormName=Regloginlive&Eventid=13674

Pittcon	American Pain Society	CLMA KnowledgeLab	AACC/ASCLS
Feb 26 - March 1	March 4-6	May 6-9	July 29-Aug 2
Orlando, FL	Anaheim, CA	Long Beach, CA	Chicago, IL

Editorial Board

Announcements:

1. **The editorial board invites ideas and article contributions for this newsletter. Please contact Dr. Pradip Datta at pradip.datta@siemens.com.**
2. There is a vacancy in the editorial board; readers are invited to join. The only qualification needed is occasional contribution on topics of our Readers' interest. If interested, please contact the Editor.