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Anna Radominska Pandya, J Clin Toxicol 2016, 6:6(Suppl)
http://dx.doi.org/10.4172/2161-0495.C1.021

7th Euro-Global Summit on

Toxicology & Applied Pharmacology

October 24-26, 2016 Rome, Italy

Natural and synthetic cannabinoids: The good, the bad, and the tragic

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K2, also called "Spice" or "Synthetic Marijuana," is a rapidly emerging drug of abuse that possesses psychoactive properties similar to those of Δ9-tetrahydrocannabinol (Δ9-THC). K2 use has exploded in many sections of the population including teenagers and first time drug users. Use of K2 can result in extreme agitation, hallucinations, supraventricular tachycardia, syncope and seizures. The presence of more than 20 different K2-aminoalkyl indoles (AAIs) have been reported in various K2s, but the two most commonly observed are JWH-018 and JWH-073; however, new generations of structurally related compounds are constantly being produced. Our studies demonstrate for the first time that the native K2s undergoes extensive metabolism by cytochrome P450s and UDP glucuronosyltransferases. Due to the activity of these enzymes, a variety of hydroxylated metabolites, have been biosythesized and excreted in human urine primarily as glucuronidated conjugates. These metabolites were identified and characterized using LC-MS/MS and HPLC-UV/Vis, and steady state kinetic analyses were also investigated. We have also shown that these K2 products cause psychoactive effects similar to those of Δ9-THC by activating CB1 cannabinoid receptors (CB1Rs) in the central nervous system. Moreover, CBRs were able to bind several hydroxylated and glucuronidated K2-AAI metabolites with an affinity similar to that of the parent compound. Finally, our *in vivo* data demonstrates that K2 metabolites retain biological activity in mice. The fact that some hydroxylated derivatives and their glucuronides can retain their biological activity makes the study of these compounds essential for understanding their severe toxicity and pharmacokinetics/dynamics. We hypothesize that the severe effects observed for some K2 users could be related to a defect in their metabolism.

Biography

Anna Radominska Pandya serves as a Professor in the Department of Biochemistry and Molecular Biology at UAMS; and she is the Editor in Chief for *Drug Metabolism Review*. She received her PhD from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw, Poland. She has published 175 papers in various peer-reviewed journals, and she has received twelve R01 grants from the NIH and DoD. Her research interests include: The regulation and suppression of human UGTs and their role as anti-proliferative agents in cancer models, the interactions between UGTs and cannabinoid receptors, the delivery of UGT genes and drugs into cancer cells using nanomaterial, and the roles of UGTs in the biotransformation of drugs including resveratrols and drugs of abuse such as marijuana and synthetic cannabinoids.

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