K42 Influence of the Genetic Polymorphism in CYP2C9 on the Pharmacokinetics of Delta-9-Tetrahydrocannabinol and Introduction of a New Pharmacokinetic Model

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After attending this presentation, attendees will understand that pharmacokinetic differences in blood concentrations of cannabis smokers depend heavily on the genetic polymorphism in the hepatic enzyme CYP2C9. Additionally, based on a new non-linear mixed-effects pharmacokinetic model developed, a simple yet highly accurate predictive model will be introduced at the presentation which allows for the estimate of time of consumption after a single consumption using Excel®.

This presentation will impact the forensic science community by stimulating the interest of forensic toxicologists to the field of pharmacogenomics and its importance to the interpretation of the analytical results (e.g., for Driving Under the Influence (DUI) cases).

Background: Medical and recreational use of *Cannabis sativa* is on the rise worldwide. There is a need for a better understanding of inter-individual differences in the pharmacokinetics of cannabinoids. Degradation of orally ingested Δ9-tetrahydrocannabinol (THC) to the pharmacologically active metabolite 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (COOH-THC) largely depends on hepatic P450 activity.[1] In this study, the impact of the CYP2C9 polymorphism on the pharmacokinetics of intravenously administered Δ9-tetrahydrocannabinol was studied in healthy volunteers who were long-time abstainers from cannabis or were cannabis naive.

Methods: Three hundred and six healthy volunteers were screened for CYP2C9 polymorphisms and phenotyped for CYP2C9 single nucleotide polymorphisms *2 (Arg144Cys) and *3 (Ile359Leu).

According to genetic subgroups, this study included 25 volunteers (11 males, 14 females). Heparinized blood samples were drawn arterially before and in short intervals up to five hours after a single intravenous bolus of 0.1mg/kg THC. Additional samples were taken from venous blood 24 and 48 hours afterward.

Sample preparation involved a liquid/liquid extraction (ethyl acetate:cyclohexane = 1:7). THC, 11-OH-THC, and COOH-THC were quantified by Liquid Chromatography with Tandem Mass Spectrometry (LC/MS/MS). The Limits of Detection (LODs) were 0.08ng/mL for THC, 0.18ng/mL for 11-OH-THC, and 1.4ng/mL for COOH-THC. The Limits of Quantification (LOQs) were 0.76ng/mL for THC, 0.48ng/mL for 11-OH-THC, and 2.0ng/mL for COOH-THC. Linearity for the 8-point calibrations extended to 600ng/mL for THC and for COOH-THC, and to 60ng/mL for 11-OH-THC. For the quantification, deuterated internal standards were used for all analytes.

Data were analyzed using Phoenix® NLME™ V1.3 and NCSS™ 8.0.14.

Results and Conclusion: Five out of eight possible different mutations were found in the 306 volunteers analyzed. Fifty-nine percent were wildtype CYP2C9*2 and *3. Δ9-THC half-times were dependent on genotypes and varied by two hours during the terminal elimination phase. There is a slow metabolizer phenotype for CYP2C9*3.

The COOH-THC metabolite accumulates to exceed the concentrations of the parent by up to 100-fold in individuals with wild type CYP2C9. These findings show there is a slow metabolizer phenotype for CYP2C9*3, which changes the metabolite ratio of THC:COOH-THC from 10:1 to 2:1. These results have consequences for the use of metabolite ratio predictive methods in forensic casework.

Genetic variability determines the pharmacokinetics of THC with impact on vital signs and psychotropic side effects. These findings will allow a more reliable interpretation of cannabinoid blood concentrations in forensic and clinical cases.

Reference:

1. Sachse-Seeboth C, Pfeil J, Sehrt D et al. Interindividual variation in the pharmacokinetics of delta-9-tetrahydrocannabinol as related to genetic polymorphisms in CYP2C9. Clin Pharmacol Ther 2009;85:273-6.

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