Urinary Clearance of 11-Nor-9-Carboxy-Δ^9-Tetrahydrocannabinol: A Detailed Pharmacokinetic Analysis

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Introduction: Urine is a common matrix for screening for cannabis use. Δ^9-Tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, is highly lipophilic, with little THC excreted in urine. Following phase I and phase II metabolism, primarily in the liver, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol-glucuronide (THCCOOH-glucuronide) is excreted as the primary urinary metabolite, accounting for greater than 95% of known urinary THC-derived compounds. The purpose of this report is to examine rigorously the relationship of THCCOOH clearance to creatinine clearance as well as the relationship of urine production (flow) rate to urine creatinine concentration and creatinine clearance as these relationships underlie the common practice of correcting THCCOOH concentrations in urine with creatinine concentrations in the same sample.

Methods: Six healthy male cannabis users were admitted to the secure residential facility at the Intramural Research Program of the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH). Spaced one week apart, cigarettes containing 0, 15.8 mg or 33.8 mg THC were smoked. All urine samples produced were collected for the next 168 h; plasma was collected based on a specific schedule[4], while urine was collected ad libitum[2]. The volume of each urine specimen was recorded as well as the time that it was produced. Urine concentrations of THCCOOH were measured by GC-MS with a limit of detection of 0.5 ng/mL. Population pharmacokinetic modeling was accomplished with Phoenix NMLE 8.3.

Results: There were 506 timed urine collections in which urine volume, creatinine concentration and THCCOOH were measured in the 6 male subjects (mean: 77.6 kg, range: 64.8-93.4 kg and mean: 31.3 years, range: 29-36 years) and included in the pharmacokinetic modeling. Our data and PK modeling indicate that cumulative urinary excretion of THCCOOH had essentially plateaued by the end of one week with less than 0.1% rise from one urine collection to the next during the final day. Our estimate of recovered dose in the urine as THCCOOH was 0.57 ± 0.35% for the low dose and 0.57 ± 0.24% for the high dose. Creatinine clearance was a significant covariate for THCCOOH clearance.

Conclusion: Our model found that only 2.2% of total THCCOOH clearance is via urinary excretion, leaving 97.8% to be accounted for by other routes of elimination. Nevertheless, creatinine clearance is a significant covariate for predicting the urinary excretion of THCCOOH. Finally, urine creatinine concentration is not highly correlated to hydration state as reflected by urine production rate, suggesting that other factors are involved in determining creatinine concentration from an isolated urine sample and that reliance on creatinine concentration or specific gravity to correct urine THCCOOH concentrations may have more limitations than previously appreciated.