MEASUREMENT OF Δ9-TETRAHYDROCANNABINOL AND CANNABIDIOL OF MEDICAL CANNABIS IN PLASMA SAMPLES AND DECOCTIONS FOR THERAPEUTIC DRUG MONITORING.

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Introduction: Medical cannabis has been authorized by the Italian Ministry of Health and cultivation and production were committed to the Military Chemical and Pharmaceutical Institute of Florence (ICFM), Italy, which produces FM2 (Δ 9-tetrahydrocannabinol, THC, 5–8% and cannabidiol CBD, 7.5–12%). THC and CBD derived from their acidic precursors, tetrahydrocannabinolic acid (THC-A) and cannabidiolic acid (CBD-A), and are formed by decarboxylation of THC-A and CBD-A, respectively. THC and CBD perform different pharmacological activity: the first display a psychotropic activity while the second seems to have analgesic and antioxidant activity and reduce THC side effects. Our previous validated Ultra High performance Liquid Chromatography-tandem mass spectrometer (UHPLC-MS/MS) method was applied in patients affected by neurological and degenerative diseases in palliative care, to determine the pharmacokinetics parameters (PK) of THC and CBD

Material and methods: The clinical study was conducted at Giannina Gaslini Institute, a tertiary care Children's Hospital in Genoa (Italy). Analyses of plasma samples and decoctions were performed by using a TSQ Quantiva™ Triple Quadrupole coupled to a Ultimate 3000 UHPLC system with atmospheric pressure chemical ionization after sample preparation with a straightforward method with deuterated internal standards. PK parameters were determined by a non-compartmental method using the 2.1Phoenix WinNonlin Professional Edition (Certara France Sarl).

Results: Ten pediatric and adult patients (4females, 6males; age range 2.5–23.2years) received an initial oral dose of THC ranging from 0.47to 0.67mg/kg/od (mean 16.4mg/day) and CBD, ranging from 0.71to 1.07mg/kg/od (mean 25.1mg/day), were enrolled. Ratios of the mean area under the curve plasma concentrations vs. time (AUC_{inf}) and each dose level (AUC_{inf}/dose), for THC and CBD, were 41.6± 22.0 and 12.5± 7.6ng/ml/minute per mg, respectively. The mean time of maximum plasma concentrations (T_{max}) was between 1and 2h and was not dose dependent for both. THC plasma concentrations are detectable until 24h and CBD until 12h. THC maximum plasma concentrations (C_{max}) ranged from 0.5to 5.7ng/ml and from 0.4to 1.9ng/ml for CBD. In all patients, THC C_{max} and AUC_{last} were higher than CBD. The mean elimination phase (K_{el}) of CBD was faster than THC. THC and CBD mean concentrations values were also measured in decoctions and the results were as follows: 22.4± 10.0 μg/ml for THC and 19.2± 7.7μg/ml for CBD, with mean extraction yields of 35± 11% and 20 ± 6%, respectively.

Discussion and conclusions: Pharmacokinetic (PK) of medical cannabis has not been extensively studied in clinical settings and there is a need to learn more information to optimize the dose-response. To date, is available only a lack of information about the variability in extraction yields and THC and CBD concentrations in decoction. Monitoring of blood levels of THC and CBD is necessary for optimization of administration of medical cannabis.