Title: Cannabinoids levels description in a cohort of patients with chronic and neuropathic pain treated with Medical *Cannabis*: a possible role of TDM

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Background:

Cannabis phytocomplex is made up of about 500 substances: in particular, Δ-9-tetrahydrocannabinol and cannabidiol, exhibit pharmacological activity, resulting in an interesting therapeutic option for many pathologies, including chronic and neuropathic pain and neurodegenerative diseases.

A few data are available in literature concerning *cannabis* pharmacokinetics, efficacy and safety of medical cannabis preparations.

Aim of the present study was the evaluation of cannabinoids pharmacokinetics in patients suffering from chronic and neuropathic pain, treated with medical *cannabis*.

Methods:

58 patients with a diagnosis of neuropathic and chronic pain were enrolled. Medical *cannabis* with THC level standardized at 19% and with a CBD level below 1% and medical *cannabis* with THC and CBD level standardized at the similar concentration of 6.5% and 8% were used.

Cannabis was administered as a decoction in 47 patients and inhaled in 11 patients. The blood withdrawn was obtained before the new dose assumption at the steady state and metabolites plasma concentrations were measured with an UHPLC-MS/MS method.

Results:

Statistically significant differences were found in cannabinoids plasma exposure between inhaled and oral medical *cannabis* with THC level standardized at 19% and with a CBD level below 1% for Δ9-THC (p=0.011), OH-THC (p=0.017), COOH-THC (p=0.004), COOH-THC-glucuronide (p=0.003) and 7-OH-CBD (p<0.001).

Regarding the role of gender in influencing cannabinoids plasma concentrations, statistically significant differences were observed between male and female, e.g. COOH-THC-glucuronide (p=0.008).

Also cigarette smoke was able to affect *cannabis* pharmacokinteic: statistically significant differences were observed between smokers and no smokers, regarding all cannabis metabolites: Δ9-THC (p<0.001), COOH-THC (p<0.001) and COOH-THC-glucuronide (p<0.001).

A correlation between Body Mass Index (Kg/m^2) and Δ9-THC plasma levels was observed (p=0.032, S=-0.300).

Demographic and pharmacological factors able to predict effective cannabinoids concentration were analysed in the logistic regression analysis: gender, inhaled *cannabis*, cardiovascular system drugs and cigarettes smoke remained in the final multivariate model.

Conclusions:

For the first time, differences in cannabinoid metabolites exposures between different galenic formulations were suggested in patients. Therapeutic drug monitoring could be useful to guide dose adjustment, but further studies in larger cohorts of patients are required to confirm these data.

Key words: Medical Cannabis, pain, THC, Cannabinoids pharmacokinetic