A POPULATION PHARMACOKINETIC STUDY OF HYDROCHLORTHIAZIDE IN HEALTHY SUBJECTS

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Objectives: To apply population pharmacokinetic (PK) modeling for the description of hydrochlorothiazide kinetics.

Methods: Hydrochlorothiazide plasma concentration (C) – time (t) data from a single dose, 2x2 bioequivalence study in 38 volunteers under fasting conditions. Nonlinear mixed effect modeling was applied in order to describe the kinetics of hydrochlorothiazide. Several structural and residual error models were evaluated. The effects of 'period' and 'treatment' were assessed for their impact on hydrochlorothiazide kinetics. Other potential variables evaluated as potential covariates were body weight, gender, height, age, creatinine clearance, glucose levels, liver enzymes, and several other biochemical laboratory values. Evaluation of the results was based on goodness-of-fit plots, statistical information criteria, and the physiological soundness of the derived parameters. The entire computational task was performed in Monolix 2016R1.

Results: A two-compartment model with first-order absorption and elimination from the central compartment was found to describe best the C-t profiles of hydrochlorothiazide. The use of a combined error model led to the optimum results, while the volumes of distribution of the central and peripheral compartments were found to be correlated one to another. The 'treatment' and 'period' effect were not significant, whereas the role of 'age' was found to be significant. In particular, as the subjects' age increased, renal clearance was found to get lower.

Conclusions: A population pharmacokinetic model was developed for the description of hydrochlorothiazide kinetics. Age is important for the determination of the pharmacokinetics of hydrochlorothiazide.