Abstract

Backgroun and aims: Pharmacokinetic variability is of paramount importance for sucessfull pharmacotherapy. The main purpose of this work was to study variability of pharmacokinetics in clinical and non-clinical setting with the aim to predict variability in target population. Specifically, three drugs were chosen, sufentanil, with relativelly narrow therapeutic index, and nabumeton and abirateron, both with known high variability.

Methods: The study of pharmacokinetic variability of sufentanil was based on clinical samples taken from patients undergoing surgical cardiac procedure, where the sufentanil was used as a part of the drug coctail used during the procedure. New analytical method was necessary to prepare and validate to measure sufentanil concentrations and obtain pharmacokinetic parameters. These were compared between determined genotype groups of MDR1 and OPRM1. Similarly, clinical study was executed with nabumetone, in which nabumetone was administered in a group of 24 subjects on two separate occassions. Plazma samples were obtained and concentrations of nabumetone and its active metabolite, 6-methoxynaphtylacetic acid (6-MNA), were determined. Obtained pharmacokinetic profiles were compared between female and male volunteers, and genotypes for MDR1 and CYP2D6. Finaly for abiraterone, new non-clinical model was needed to evaluate novel drug formulations and to predict its absorption in man.

Results and conclusion: Novel analytical method, liquid chromatography with MS/MS detection, for sufentanil measurements in human plazma was validated and used to measure sufentanil concentrations in plasma samples of 25 patients. No differences were seen between genotypes for MDR1 or OPRM1. In clinical study with nabumetone, some differences were seen between female and male volunteers, specifically in clearance and AUC of 6-MNA, on the other hand no differences were seen for any nabumetone parameters, nor between genopypes for MDR1 and CYP2D6 in neither of the substances. Incomplete block design was used in the non-clinical study with abiraterone to compare 4 drug formulations in rats, the original formulation with problematic and variable absorption, positive control, also a positive control for which enhanced exposure to abiraterone was already described, and two new drug formulations. Blood samples were collected via catheter, that was inserted during a surgical procedure, and concentrations of abiraterone was measured in obtained plazma. Calculated pharmacokinetic profiles shown 250% increase in

abirateron exposure with novel drug formulations. This model can be used for fast and relatively cheap evaluation of new drug formulations.

Key words: Personalized medicine, pharmacokinetic variaibility, nabumetone, abiraterone, sufentanil, pharmacogenetics, clinical study, non-clinical study, liquid chromatography