

Population Approach Group of India (PAGIN) 2013: A Report

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Population Approach Group of India (PAGIN) is a non-profit organization focused on the training of pharmacometric community in India. Pharmacometrics is a science that specializes in data analysis and modeling using mathematical and statistical methods for handling pharmacokinetic (PK), pharmacodynamics (PD) and disease progression models. The present workshop is the sixth workshop of PAGIN from its inception in the year 2008. Every year experts in the field of pharmacometrics and aspirants of pharmacometric expertise come together at the PSG Institute of Medical Sciences and Research at Coimbatore, India for learning and discussion. This year's workshop was conducted between 1st and 3rd of August. Dr. Mallika Lala, Pharmacometric consultant, Dr. Balaji Agoram, Director, Med Immune Inc, Cambridge, UK and Dr. Surulivel Rajan, Assistant Professor, Manipal College of Pharmaceutical Sciences, Manipal, India were the trainers. Totally there were 30 participants and program had lectures and hands-on-component. Three abstracts were presented during the workshop in the area of PK-PD modeling by the participants. These three abstracts highlight the kind of work which can be carried out using this new pharmacometric approach. The first abstract explains population pharmacokinetic approach in which bio-equivalence study data is used to develop a pharmacokinetic model and to study the impact of various covariates

on the pharmacokinetics. This population based approach offers better alternative to traditional Non compartment Analysis. The second abstract explains how the population pharmacokinetic model is used to develop new simulations which predicts steady state concentrations in patients with various dosage regimen and assess the impact of various factors on the pharmacokinetics. Such predictions will have a role in clinical settings where new dosage regimens are explored for their utility and safety. The third abstract is based on a work to explore the impact of drug-herbal interaction and assess the intensity of such effect on the pharmacokinetics. The NONMEM approach provides the quantitative assessment of drug interactions with the inter and intra patient variability.

The pharmacometrics is a very new discipline with people from broad areas of interest working together. This approach needs training in system biology, pharmacology, pharmacokinetics, mathematics and statistics with some level of programming skills. Although it is a daunting task for a beginner, with the availability of training and support, many aspirants take up research in this area. PAGIN is providing such platform for training and interaction.

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Population pharmacokinetics of oral escitalopram in healthy Indian adults: Application to evaluate bioequivalence for two different formulations

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Escitalopram, the S-enantiomer of the antidepressant citalopram, is one of the most commonly prescribed selective serotonin reuptake inhibitors. After oral administration, maximum plasma concentrations are reached in about 4 hours. The half-life of escitalopram is 27 to 32 hours. Therefore it is commonly given once daily. No reports on the pharmacokinetics (PK) properties of escitalopram in Indian population have been identified. Therefore, in this study, we sought to develop a population PK model for escitalopram in healthy Indian male subjects and to compare the PK characteristics with other populations.

Traditional Non-Compartment Analysis based bio-equivalence (BE) assessment method suffers from lot of limitations. To overcome these limitations Non-Linear Mixed Effect Model (NLMEM) based BE assessment method was selected in which PK data is analyzed using NLMEM and further bioequivalence tests are performed on individual estimates of AUC and C_{max} obtained from NLMEM. We applied this methodology of NLME based BE assessment for the comparison of two different oral formulations to investigate whether both formulations are bioequivalent.

A randomized, two-period, crossover bioequivalence study was performed in 12 healthy Indian male subjects. All subjects received either the test or reference

formulation as a single 20-mg oral dose of escitalopram with a 2-week washout period. Blood samples were collected at 0 (predose), 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 156 hours after dosing. Plasma escitalopram concentrations were analyzed using UPLC/MS/MS. A population PK analysis was performed using plasma concentration data from both formulations through NONMEM (Ver. 7.2), PLT Tools (ver 4.6), R (ver 3.0) and XPOSE-4 (ver 4.4).

A one-compartment model with first order absorption and first-order elimination (ADVAN 2 TRANS 2) described the best fit to a total of 312 concentrations. Structural model was developed in the first-order conditional estimation with interaction method. The influence of demographic characteristics on PK parameters was examined. The best structure of PK model explaining the time concentration profile was identical in both oral escitalopram formulations. There were no significant covariates affecting PK parameters. The final structural model was validated through the visual predictive check and bootstrap with no serious model misspecification.

Thus, a population PK model was developed and reasonable parameters were obtained from the data of healthy Indian male subjects.

ABSTRACT- 2

Designing the dosage regimen for valproate therapy through simulations using NONMEM

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The variability of study state concentration of drugs (valproate) always exists while treating the patients with standard dosage regimen so there is a need to understand and detect the variability and modify the therapy. The population pharmacokinetic (POPK) model for valproate is already available in the literature. The covariates which were included in the final PK model for valproates were gender and concomitant use of phenytoin. The variability could be because of covariates which influence the steady state concentration. Using the same POPK model, simulations were performed using NONMEM software package employing PIRANA version 2.5.0 as front end application for with 400 mg, 500 mg,

800 mg, 1000 mg of valproate. The criteria like median steady state concentration (C_{ss}) and number of patients with C_{ss} within the therapeutic range were considered for interpretation. 500 mg twice daily dosage regimen was found to be more advantageous as more number of simulated patients were having the C_{ss} within the therapeutic range and the effect of covariates like sex and concomitant phenytoin use were found to be insignificant but with 1000 mg once daily regimen in females, the number of individuals with C_{ss} within the therapeutic range were found to be less. This might be due to the inducing effect of phenytoin on valproate metabolism in females which could be more than that of males.

ABSTRACT- 3

Poppk Modeling of herb-Pgp interactions: Effect of capsaicin on oral fexofenadine in healthy male volunteersVijay Kumar Sripuram^{1,2,3}, Harish K. Kaushik^{1,3}, Narsimha Y. Reddy³¹ Department of Pharmacology, IST, JNTU Hyderabad, India.² Dr. Reddy's Institute of Life Sciences, University Of Hyderabad, Hyderabad, India.³ Department of Pharmacology, UCPSc, Kakatiya University, Warangal, India.

A population pharmacokinetic (PopPK) model for capsaicin effect on fexofenadine, a probe p-glycoprotein (Pgp) substrate, was developed using Phoenix NLME (1.2). A single dose of fexofenadine-120 mg was orally administered to 12 healthy male subjects in two phases, who were pre-treated with placebo and capsaicin in first and second phases respectively for 10 days till dosing. Concentrations of fexofenadine from 336 plasma samples were determined by newly developed LC-MS/MS method.

A two compartmental model with first order

kinetics was chosen after exploratory analysis using phoenix Winnonlin (6.3). Proportional error model was used to describe inter individual variability in FOCE-ELS phoenix engine. The influence of co-medication was highly significant on clearance (Cl) and volume of distribution (Vd) in both compartments. The population mean values of CL, CL2, Vd and Vd2 were 32 L/h, 4 L/h, 92 L and 13 L respectively. The results of this study show the importance of recognizing the inhibition of systemic clearance (decrease in CL) and modulation of volume of distribution when using the PopPK approach.
