Abstract:

The therapeutic window of any drug is only a generalization. The concept of ‘one dose fits all patients’ has given way to ‘individualized therapy’ according to the unique genetic makeup of the patients. CYP2C19 genetic polymorphism is found to be more prevalent in Asian population and specifically in south Indian population. Population Pharmacokinetics is an approach to quantify inter and intra individual variability in drug concentrations in a specific patient population. The aim of this study was to investigate the impact of CYP2C19 genetic polymorphism on population pharmacokinetics of selected drugs: sertraline and omeprazole in south Indian population. The study was approved by the IRB of JSS College of Pharmacy, Ooty and conducted in compliance with the principles of good clinical practice. Blood samples at predetermined time points were collected from the patients who attained the steady state concentration of the study drugs. The plasma concentration of drug and metabolite were quantified by validated high performance liquid chromatography method. The genetic polymorphism was determined by reverse transcriptase polymerase chain reaction and restricted fragment length polymorphism methods. The data of 104 and 105 patients on sertraline and omeprazole respectively were analyzed and the frequency of poor metabolizer allele (*2/*2, *3/*3) in the study patients (n=209) ranged between 12-15 % with an average of 13.4 % which is comparable with earlier reports in this population. The frequency of mutation for *2 (35%) was greater than the *3 (1%). The drug to metabolite ratio of sertraline at t\text{max} had shown a significant (p<0.05) difference between poor metabolizers and extensive metabolizers. Clearance and volume distribution of sertraline were calculated as 76.8 L/h and 1870 L with the variance of about 68 % and 54 % respectively in the base model which was reduced to 16 % and 18 % after adding age and genetic polymorphism as covariates to influence the clearance. Such parameters of omeprazole were calculated as 26.3 L/h and 31.1 L respectively with the variance of about 36 % and 23 % and were reduced to 13 % and 12 % in the final model after adding age and genetic polymorphism as covariates to influence the clearance. The final models were validated by using bootstrap methods and visual predictive checks. Thus, the present study had explained the influence of age and genetic polymorphism (*2&*3) of CYP2C19 on the pharmacokinetics of the study drugs, sertraline and omeprazole in the study population. A complete PK-PD modeling study need to be conducted for the study drugs to confirm the clinical implications of these findings.