The factors determining variations in response to medications are complex and interdependent. Among them, racial and ethnic groups comprise important populations whose special needs and drug responses traditionally have been undervalued or ignored. Genetic phenotyping as poor metabolizer or extensive metabolizer is one of the important factors that may influence the primary pharmacokinetic parameters like clearance and volume of distribution that in turn may influence the terminal elimination constant, biological half-life, time to reach steady state, etc. Though genetic polymorphisms in many CYP 450 enzymes have been reported almost in all ethnic population, the frequency of \textit{CYP2C19} polymorphism especially poor metabolizer genotypes is reported as high in south Indian population than the Caucasian population. Hence the influence of this genetic polymorphism on the substrate drugs is a concern for investigation.

Sertraline is known to be metabolized by this isoenzyme to a larger extent, though the other enzymes do play a role in the metabolism of this drug. High inter-individual variability was reported in sertraline pharmacokinetics in other Asian population except Indians. Hence, in this study interest was shown to investigate the impact of the \textit{CYP2C19} genetic polymorphism on the pharmacokinetics of sertraline.

Omeprazole is a drug approved by USFDA as a probe drug to phenotype \textit{CYP2C19} metabolic activity and it has been advised to be extra alert about insufficient clinical response and recommend considering dose increase by 100-200%. It was also proven that the treatment to H. Pylori infection seemed to be successful in the poor metabolizers and very high failure ratio observed in the extensive metabolizers. Moreover controlled clinical trials have proven that higher exposure to omeprazole concentration will cause achlorhydria and calcium malabsorption leading to multiple
fractures in acute and chronic conditions respectively. Omeprazole is a most commonly used PPI in India especially in the government health care set up. Hence, this has been chosen as the second drug to be investigated.

A statistically significant (p < 0.05) reductions (48 % to 42 %) were observed in the drug to metabolite ratio of sertraline and desmethylsertraline in poor metabolizers at peak time, 5 and 6 h respectively. This reveals that there is a remarkable difference in the metabolism of sertraline between poor metabolizers and extensive metabolizers based on CYP2C19 genetic polymorphisms and CYP2C19 enzyme may be an important determinant of the pharmacokinetics of both sertraline and desmethylsertraline. This in turn may have possible relevance in therapeutic / safety outcome of sertraline. Age has been identified as another important factor influencing the clearance and so the pharmacokinetics of this drug. The drug metabolite ratio of omeprazole was not investigated in this study as the pure metabolite sample was not available with us.

Population pharmacokinetic approach, a industrial standard statistical procedure recommended by the regulatory agencies like USFDA is adopted to investigate the influence of various covariates including genetic polymorphism. The base model was first developed and the influence of various covariates was tested by the methodical approach to achieve the final model. Age and genetic polymorphism were found to be the covariates influencing clearance of both these study drugs. It is also noted that age has much more pronounced impact on the clearance of these two drugs than genetic polymorphism. Based on the final population models and estimated primary pharmacokinetic parameters, appropriate dosage guidelines for these drugs in this population could be derived.
Based on the results obtained from the present study, including both the study group patients (n=209), the frequency of poor metabolizer allele (*2/*2, *3/*3) in the study patients ranged between 12-15 % with an average of 13.4 % which is comparable with earlier reports in this population. The frequency of *2 type mutation (35%) was greater than the *3 (1%) mutation.

The impact of these genotypes on the population pharmacokinetic parameters of any drug(s) is not studied so far in Indian population. This study made an attempt to include the CYP2C19 polymorphic phenotype as a covariate in the population pharmacokinetics model to explore the significant role of this metabolizing enzyme.

To conclude, the present study has 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. The pharmacometric analysis was carried out to quantify the extent of influence of these covariates on the pharmacokinetic parameters and final mathematical model was derived. The clearance that could be calculated by using the final model needs to be correlated with the dosage calculation in order to study the clinical impact.

The limitations of the present study include the concentration of 5-hydroxy omeprazole, the major metabolite of omeprazole could not be measured. Due to processor capacity limitation, simulation of the final data could not be done. The findings of these studies revealed only the pharmacokinetic aspects of the drugs. Further, the same should be validated in clinical settings by taking the pharmacodynamic parameters into consideration. The other substrates of this isoenzyme may also be critically studied in this population.