“Every individual is different from another and hence should be considered as a
different entity. As many variations are there in the universe, seen in human being”

– Charaka, 4000 years ago.

“If it were not for the great variability between individuals, medicine might as well be a
science, not an art”


We proudly say that all humans are alike. This may be true only as a species. In realism, dramatic differences exist among humans with respect to their race, ethnicity, age, gender, anthropometry, social habits and etc. including their response to drugs. In order to achieve the optimal safety and efficacy of drug treatment, the concept of ‘one dose fits all patients’ has given way to ‘individualized therapy’ according to the unique genetic makeup of the patients. Pharmacogenetics and Pharmacogenomics are the imminent concepts in modern medical science paving the way towards individualized therapy. The salient feature of pharmacogenetics is, it’s potential to explain the cause for unexpected drug response, either efficacy or safety issues. On the other hand, pharmacogenomics explicitly explores the genetic differences within a population to explain certain observed response to drugs or susceptibility to a particular disease.

Individualized therapy has the following three aspects: identifying a population subgroup that is more likely or less likely to respond, identifying the subgroup more prone to adverse drug reactions and defining better dose. To reveal these aspects, different approaches have been adopted and among them, some have been standardized (e.g. studies on drug metabolizing enzymes) while others are still exploratory.
Clinically significant variability in therapeutic response has been linked to genetic factors for drugs like Warfarin, Codeine, Thiopurines and Phenytoin which showed variability in pharmacokinetics based on genetic polymorphisms of metabolizing enzymes. \textsuperscript{6-8}

‘Guidance for Industry on drug metabolism / interaction: \textit{in vitro}’ published by United States Food and Drug Administration (USFDA) states, “Identifying metabolic differences in patient groups based on genetic polymorphisms could help and guide the design of dosimetry studies for such population groups”. \textsuperscript{9} USFDA has also published guidance on ‘Pharmacogenomic Data Submissions’ with the intention to guide development of pharmacogenomics to benefit both drug development programmes and public health. \textsuperscript{10} As per the International Conference on Harmonisation (ICH) guidelines: E-5, companies need to perform a ‘bridging study’ showing efficacy and safety data to make earlier large scale foreign trial data admissible in other regions. \textsuperscript{11} It is also the researchers’ general opinion that “pharmaceutical companies not applying pharmacogenomics will struggle to survive in the global market in the next 20 years”. \textsuperscript{12}

In light of these facts, it is evident that, drug therapy for specific populations and patients should be individualized to achieve the most effective health outcomes. The therapeutic window of any drug is only a generalization. The plasma/serum concentrations of a drug that determine the therapeutic window are average values in which most patients, but certainly not all respond similarly. In future, the potential of pharmacogenetics will be the design and development of drugs, their dosage regimen and its therapeutic window that work well with individuals or certain population groups. \textsuperscript{13} Hence, individualized drug therapy should begin by setting such a specific individualized
target and the task of the clinicians will be to select, and then to hit the desired target as precisely as possible instead of applying ‘cook book’ drug therapy. It is advocated that the therapy should be individualized for specific populations and patients, at least for ‘narrow therapeutic index drugs’ as even a small change in systemic concentration of such ‘critical dose drugs’ can lead to remarkable change in pharmacodynamic response. Characteristically, these drugs will cause serious clinical consequences if over dosing or under dosing occur and warrant monitoring blood concentrations and need to be dosed on the basis of individualized parameters.

The individual factors that determine the variations in response to drugs are complex and interdependent which include cultural factors (e.g. attitudes, beliefs of an ethnic group), environmental factors (e.g. diet, climate, smoking, alcohol, pollutants) and chiefly biological factors (e.g. age, gender, body weight, genetic polymorphism). Genes are considered to be functionally polymorphic and such polymorphism alters the activity of the gene product which is typically a protein such as a drug metabolizing enzyme or a drug receptor. Polymorphisms affecting the response to drugs can occur in genes involved in one of three processes viz. drug metabolism, drug targets, and the disease pathway.

Of these three mechanisms, polymorphisms in drug metabolism genes are considered most important because they act across classes of drugs. Metabolisms of drugs are mainly performed by one of several oxidative enzyme systems associated with Cytochrome P450 (CYP 450). These enzymes are now referred by their genetic names viz. CYP2C9, CYP2C19, CYP2D6, CYP3A4 and etc. Polymorphic variants in these genes.
alter the activity of the encoded enzyme most often by reducing it, sometimes by eliminating it, and occasionally by enhancing it. Although there are polymorphisms in all genes controlling drug effects, they do not necessarily alter drug response and do not necessarily show significant variation among populations. Those individuals who do not metabolize a certain drug efficiently are called “Poor Metabolizers” (PM), as opposed to normal or “Extensive Metabolizers” (EM). The PMs may get increased exposure to the active drug and toxicity by reduced clearance and enhanced peak concentration in the blood.

Thus, identifying sources of variability in pharmacokinetics of drugs is imperative in the clinical management and may aid in optimal dosage selection. Population pharmacokinetics is an approach to quantify determinants of drug concentrations in a specific patient population. It can be defined as the study of the sources and correlates of variability in drug concentrations among individuals who represent the target population that ultimately receives relevant doses of drug of interest. The use of population approach for doing pharmacokinetic analysis has increased during the last fifteen years. In contrast to traditional pharmacokinetic analysis, the population pharmacokinetics obtains relevant pharmacokinetic information in patients who are representative of the target population. In addition, it identifies and quantifies the sources of variability that contributes to differences between expectations and outcomes. The source variability is categorized as inter-individual variability and residual variability.

Inter-individual variability is the biological variability that exists between subjects. Searching for covariates that can account for some of the inter-individual
variability is another important feature of population pharmacokinetics. Covariates can be patient demographic features such as age, gender and body weight, environmental factors, genetic phenotypes, drug-drug interactions and physiologic factors such as renal impairment.\textsuperscript{22,23} Residual variability is, variability due to errors in concentration measurements, misspecifications of the model, inexplicable day-to-day or week-to-week variability (i.e. inter-occasion variability) and intra-individual variability.

Contemporary India is a land of enormous human genetic, cultural and linguistic diversity. Based on serum protein, red cell enzyme markers etc. it has been proven that with the exception of Africa, India harbors more genetic diversity than other comparable global regions.\textsuperscript{24}

Though there are about more than 50 enzymes in CYP450 family, only six of them, viz., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 are known to be responsible for the metabolism of more than 90 per cent of the drugs used clinically.\textsuperscript{25} USFDA included the pharmacogenomic biomarker information of certain metabolizing enzymes in the labels of selected drugs.\textsuperscript{26} Literature search has revealed that among the genes encoding these six enzymes, genetic polymorphism of CYP2C19 is found to be more prevalent in Asian population and specifically in south Indian population.\textsuperscript{27,28}

Sertraline, a selective serotonin reuptake inhibitor (SSRI) is the substrate of CYP2C19 isoenzyme and shown high inter individual variability in its disposition and clinical response in Chinese subjects.\textsuperscript{29} Omeprazole, an another substrate of this enzyme is the most commonly prescribed proton pump inhibitor (PPI) in Indian health care set up.
and known to show remarkable differences in pharmacokinetic and pharmacodynamic aspects in relation to genetic polymorphism of the CYP2C19 enzyme in different populations.\textsuperscript{30-36}

In spite of these facts, the influence of \textit{CYP2C19} genetic polymorphism on the pharmacokinetics of these two drugs has not been studied in south Indian population. Hence, in the present work, the impact of \textit{CYP2C19} genetic polymorphism on pharmacokinetics of sertraline and omeprazole is investigated in south Indian population using population pharmacokinetic approach.