

Effect of polymorphism in CYP2C19 on Pharmacokinetics of Omeprazole in Indigenous Population

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Abstract— Omeprazole, a proton pump inhibitor (PPI) is one of the most widely prescribed drugs used world wide and is available over-the-counter in some countries. According to the results of numerous clinical studies, *CYP2C19* polymorphisms is an important factor affecting the pharmacokinetics of most PPIs. According to some research, Asian populations is characterized by high prevalence of defect *CYP2C19* alleles. But there is no data available about genotyping of our population. That shows the importance of pharmacogenomics before pharmacokinetic and bioequivalence studies in our population. In this study the pharmacokinetic parameters of omeprazole in 200 human volunteers (100 male and 100 female) are evaluated and the genetic polymorphism of allele *CYP2C19* by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) are identified. So that by finding and identifying genotypes of every participant it is evaluated that whether the volunteers are extensive, intermediate or poor metabolisers and variation among their pharmacokinetic parameters are compared. In Pakistan where people belong from different cultures and races, evaluation of genetic polymorphism is essential for minimizing the adverse effects and calculating the accurate dose of drug.

Keywords- Omeprazole, genotyping, pharmacokinetics, genetic polymorphism

I. INTRODUCTION

Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome. Omeprazole is one of the most widely prescribed drugs internationally and is available over-the-counter in some countries. It is a selective and irreversible proton pump inhibitor. It suppresses stomach acid secretion by specific inhibition of the H⁺/K⁺ ATPase system found at the secretory surface of gastric parietal cells. Because this enzyme system it is regarded as the acid (proton, or H⁺) pump within the gastric mucosa, omeprazole inhibits the final step of acid production. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. Absorption of omeprazole is rapid, with peak

plasma levels occurring within 0.5 to 3.5 h. The absorption of omeprazole takes place in the small intestine and is usually completed within 3–6 hr. The systemic bioavailability of omeprazole after repeated dose is about 60%. [3]

According to the results of numerous clinical studies, *CYP2C19* polymorphisms is an important factor affecting the pharmacokinetics of most PPIs. Interindividual differences in plasma concentrations of these proton-pump inhibitors may be prospectively predicted by genetically determined *CYP2C19* status [2]. Therefore genotyping for *CYP2C19* polymorphisms should be recommended, first of all in Asian populations characterized by a high prevalence of defect *CYP2C19* alleles. Genetic polymorphism exists for *CYP2C19* expression, with approximately 3–5% of Caucasian and 15–20% of Asian populations being poor metabolizers with no *CYP2C19* function [5]. This may reduce the efficacy of clopidogrel and can become threatening for heart patients [4]. The results of prospective controlled clinical trials need to be awaited to see whether patients might benefit from such individually tailored therapy. Through pharmacogenetics there has been a dramatic increase in the amount of genomic information that is available. This information provides the necessary data for comprehensive studies of individual genes and broad investigation of genome-wide variation. [7]. So in Pakistan where people belong from different cultures and races, evaluation of genetic polymorphism is essential for minimizing the adverse effects and calculating the accurate dose of drug.

II. RESEARCH OBJECTIVE

The aim of this study is:

A. To investigate gender and polymorphisms in *CYP2C19* in indigenous population.

B. To determine the pharmacogenetics of every participant by finding their genotypes and identify whether the volunteers are extensive, intermediate and poor metabolisers

III. REVIEW OF LITERATURE

It has been studied that the influence of dose on the kinetics of omeprazole and two of its metabolites, hydroxyomeprazole and the sulphone. Ten healthy subjects were given omeprazole 10 and 40 mg iv and 10, 40 and 90 mg orally. No significant dose-related difference in any parameter calculated from the iv experiments was detected. Following the oral solutions, however, there was a dose-dependent increase in systemic availability, probably due to saturable first-pass elimination. The AUC of the sulphone also seemed to increase non-linearly with increasing dose, and that of the hydroxyomeprazole increased in proportion to dose. The slight dose-dependency of the bioavailability of the solution is considered to be of no or limited clinical relevance. Furthermore, since omeprazole is given orally as slowly absorbed enteric coated granules in the dose of 20 mg o.d., the potential for dose-dependent kinetics in clinical practice would be much less.[2]

It has been determined that Omeprazole has actual adverse influences on the pharmacokinetics of medications such as diazepam, carbamazepine, clozapine, indinavir, nelfinavir, atazanavir, rilpivirine, methotrexate, tacrolimus, mycophenolate mofetil, clopidogrel, digoxin, itraconazole, posaconazole, and oral iron supplementation. Meanwhile, low efficacy of omeprazole treatment would be anticipated, as omeprazole elimination could be significantly induced by comedicated efavirenz and herb medicines such as St John's wort, Ginkgo biloba, and yin zhi huang. The mechanism for DDI involves induction or inhibition of cytochrome P450, inhibition of P-glycoprotein or breast cancer resistance protein-mediated drug transport, and inhibition of oral absorption by gastric acid suppression. Sometimes, DDIs of omeprazole do not exhibit a PPI class effect. Other suitable PPIs or histamine 2 antagonists may be therapeutic alternatives that can be used to avoid adverse consequences. The degree of DDIs associated with omeprazole and clinical outcomes depend on factors such as genotype status of CYP2C19 and CYP1A2, ethnicity, dose and treatment course of precipitant omeprazole, pharmaceutical formulation of object drug (eg, mycophenolate mofetil versus enteric-coated mycophenolate sodium), other concomitant medication (eg, omeprazole-indinavir versus omeprazole-indinavir-ritonavir), and administration schedule (eg, intensified dosing of mycophenolate mofetil versus standard dosing). Despite the fact that omeprazole is one of the most widely prescribed drugs internationally, clinical professionals should enhance clinical risk management on adverse DDIs associated with omeprazole and ensure safe combination use of omeprazole by rationally prescribing alternatives, checking the appropriateness of physician orders before dispensing, and performing therapeutic drug monitoring.[11]

It also has been found that Omeprazole and lansoprazole can be given in sodium bicarbonate. However, lansoprazole 30 mg as simplified lansoprazole suspension produced an effect similar to that seen with intact capsules. The absorption of both drugs when given orally as capsules or as

suspensions in sodium bicarbonate are evaluated. There was impairment of omeprazole absorption when given as simplified omeprazole suspension. Maximum plasma concentration and area under the concentration/time curve were lower with simplified omeprazole suspension than with omeprazole capsules ($P=0.034$ and 0.013 , respectively, on day 5). No differences were found in lansoprazole absorption when simplified lansoprazole suspension was compared with its standard capsule formulation. Relative bioavailability of omeprazole from simplified omeprazole suspension compared to the capsule was 58.4% on day 5. The corresponding value for lansoprazole was 84.7%. Simplified omeprazole suspension 20 mg does not supply adequate omeprazole for systemic absorption. Lansoprazole absorption from simplified lansoprazole suspension is maintained.[8]

A comparative pharmacokinetic study with each PPI was designed as an open, randomized, and crossover study of 18 Japanese healthy volunteers who were classified into the homozygous, heterozygous extensive metabolizer and the poor metabolizer based on the CYP2C19 genotype determined by PCR-RFLP method. Each subject received a single oral dose of 20 mg omeprazole, 30 mg lansoprazole, or 20 mg sodium rabeprazole, with at least 1 week washout period between treatments. Plasma concentrations of PPIs and their metabolites were monitored until 12 h after medication. Pharmacokinetic profiles of omeprazole and lansoprazole were well correlated with the CYP2C19 genotype. The heterozygous extensive metabolizer was slightly different from the homozygote, but there was no statistically significant difference. The CYP2C19 genotype dependence found for lansoprazole was not obvious compared with omeprazole. As for rabeprazole, the pharmacokinetic profile was independent of the CYP2C19 genotype. CYP2C19 genotype dependence will be found in the anti-H. pylori therapy even when lansoprazole is used as the PPI.[10]

The pharmacokinetic (PK) of omeprazole (OMP), 5-hydroxy-omeprazole (5-OH-OMP) and omeprazole sulphone (OMP-SUL), was investigated in healthy premenopausal and postmenopausal females. A single oral dose, open-label, non-controlled, pharmacokinetic study was conducted in healthy premenopausal ($n = 16$) and postmenopausal ($n = 8$) females. The samples were analyzed using reversed phase high performance liquid chromatography (HPLC), different pharmacokinetics (PK) parameters were determined and compared statistically to evaluate the difference between two groups. The activities of CYP2C19 and CYP3A4 were determined as $AUCOMP/AUCOH-OMP$ and $AUCOMP/AUCOMP-SUL$, respectively. The significant differences ($P < 0.05$) between C_{max} , t_{max} , $t_{1/2}$ and metabolite ratios (MR) of OMP, 5-OH-OMP and OMP-SUL were observed between premenopausal and postmenopausal females. The present studies showed the higher AUC and longer $t_{1/2}$ in postmenopausal subjects. The increase in MR for 5-OH-OMP and also OMP-SUL determined as $AUCOHOMP/AUCOMP$ and $AUCOMP-SUL/AUCOMP$,

respectively, was also observed in postmenopausal females compared with the premenopausal females.[9]

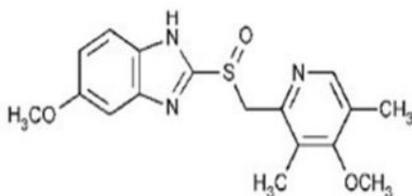


FIGURE 1 – Structural formula of omeprazole.

III. PROPOSED METHODOLOGY

A. Selection of Volunteers

70 healthy male and 70 healthy female volunteers are selected. Only those volunteers are selected, who are of age between 20-40 year, who are not suffering from any disease especially liver diseases, who are not taking any medication before starting the study, who are non smokers. Written consent are taken from the volunteers. Complete blood profile and family history are taken and the volunteers are clearly informed about the objectives of study, the frequency of blood sampling and the possible side effects which they may face during the study. Prior approval from ethical committee will also be obtained.

B. Procedure

All the volunteers are kept on NPO (Nil Per Oral) for at least twelve hours before and six hours after the drug treatment. A 20mg tablet of omeprazole will be administered orally to each individual with 200ml of water. After the administration of the drug, a forearm of each volunteer is cannulated for blood sampling. A sterile venous cannula with in-stopper 22G aseptically inserted in the vein. 5ml blood samples are collected in heparinized test tubes at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 hours through 5CC syringe from each individual. Plasma is separated by centrifugation at 10000 RPM for 10 minutes and after separation plasma fractions are transferred to labeled glass tubes and stored in a deep freezer at -40°C till analysis.

C. Analysis

The separation is achieved on C18 column using isocratic flow. The analysis is performed on HPLC. The mobile phase will be a mixture of potassium dihydrogen phosphate buffer (pH 7.2 ± 0.05; 0.2 M) and acetonitrile (70:30, v/v), pump at a flow rate of 1.0 ml/min through the column at room temperature. The mobile phase is degassed prior to use under vacuum by filtration through a 0.2µ nylon

membrane. Concentrations are measured at 302 nm by UV detector at a sensitivity of 0.0001[6]. A stock solution of omeprazole 1mg/ml is prepared by dissolving 100mg of omeprazole in 100ml of distilled water. The standard solutions of 1000, 500, 200, 100, 50, 20, 10, 5 ng/ml are prepared by spiking the blank plasma of respective species with stock solution of omeprazole

Omeprazole is extracted from plasma by using organic solvents. To 1ml of plasma sample 1ml of ethanol is added. The High speed vortex mixing for 1-2 minute is used for efficient extraction. The samples are centrifuged at 4500 RPM for 15 minutes. An aliquot of 1 ml of protein-free supernatant is evaporated to dryness at 45°C under nitrogen. The residue is reconstituted in 200 µl of mobile phase and 20 µl of which will be injected into HPLC system for the analysis [6]. Pharmacokinetic parameters like Area under the Curve (AUC), Peak Plasma Concentration (C_{max}), Time to reach peak plasma concentration (t_{max}), Plasma half life ($t_{1/2}$), Volume of distribution, Total body clearance are measured. Calculation of all the pharmacokinetic parameters are done by entering plasma concentration-time data in software APO pharmacological analysis MW/PHARM version 3.02. The mean and standard deviation of pharmacokinetic parameters of Carvedilol in healthy volunteers were determined by standard statistical method [7].

IV. CONCLUSION

It has been concluded that genotyping and phenotyping for CYP2C19 activity can be an important clinical tool contributing to better treatment of efficacy. So it is very important to have a complete genetic picture of our population.

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