PHARMACOKINETIC DRUG-DRUG INTERACTION STUDY OF VORICONAZOLE WITH CLARITHROMYCIN

BY

MEHWISH MUSHTAQ

Synopsis submitted to Abdul Wali Khan University Mardan in the partial fulfillment of the requirements for the degree of

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Session (2017 – 19)

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DEPARTMENT OF PHARMACY
FACULTY OF CHEMICAL & LIFE SCIENCES
ABDUL WALI KHAN UNIVERSITY MARDAN

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RESEARCH PROPOSAL FOR M. PHIL IN PHARMACY

TOPIC: PHARMACOKINETIC DRUG-DRUG INTERACTION STUDY OF VORICONAZOLE WITH CLARITHROMYCIN

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DEPARTMENT OF PHARMACY

ABDUL WALI KHAN UNIVERSITY, MARDAN

1. INTRODUCTION

Drug-drug interaction (DDI) occurs when one drug (perpetrator drug) varies the plasma concentration and the biological outcomes of the second drug (victim drug). Pharmacokinetic drug-drug interaction (PK-DDI) may occur at the level of absorption, distribution, metabolism, or excretion when a co-exposed drug may result in alteration of blood-concentration vs. times profile of one or both drugs. Induction of CYP450 enzymes by the co-administered drug results in a decrease in substrate drug concentration leading to in-efficacy or inhibition of CYP450 enzymes by another drug resulting in prolonged half-lives and/or higher substrate drug concentration that may enhance the potential for side effects. Drug transporters also play a vital role in drug disposition when both co-exposed drugs have an affinity for the same binding site of the transporter, while age, gender, nutritional status, various diseases, genetic polymorphisms, and ontogeny of the metabolic enzyme may also affect the drug metabolism **(Müller and Fromm, 2011, Michalets, 1998)**.

Voriconazole is synthetically derived from fluconazole antifungal. Voriconazole **(Fig. 1)**, chemically is ([2R, 3S]-2- [2, 4-difluorophenyl]-3-[5-fluro-4pyrimidinyl]-1- [1 H -1, 2, 4-trizole-1-yl]-2-butanol) and has a broad spectrum categorized as second-generation triazole antifungal. Voriconazole is also called a 14-alpha-sterol demethylase inhibitor, broadly used to manage invasive Aspergillosis and other serious fungal infections. Voriconazole binds to the rate-limiting enzyme and inhibits the CYP450 enzyme, leading to inhibition of ergosterol synthesis and deposition of 14-alpha-methyl sterols such as lanosterol, so the structure of fungi cell membrane disrupts. Voriconazole is a strong inhibitor of CYP51 (fungal CYP enzyme) as compared to fluconazole. It has additional activity against Candida Albicans, Candida kurusei Scedosporium, Fusarium, and certain other emerging pathogens. Usually, the first oral administered dose of voriconazole is 400mg, followed by a maintenance dose of 200mg at a 12hr dosing interval, and in some conditions, the loading dose is maintained at 9mg/kg, twice a day (BD). Voriconazole is rapidly absorbed and has mostly 96% oral bioavailability. The Peak plasma concentration (C_{max}) of voriconazole is 5.27mg/L at 400mg and the

target is achieved in 1-2hr after drug administration. Both C_{max} and AUC are dose-proportional over the range of (200mg-400mg). The volume of distribution is 4.6L/Kg and plasma protein binding is 58%. Terminal elimination half-life ($t_{1/2}$) ranged from 8hr to 15hr and there is no effect over the steady- pharmacokinetics of voriconazole by variation in the timings of administration of dose (morning or evening). Voriconazole is highly metabolized by the hepatic enzyme CYP2C19 and forms a voriconazole-N-oxide as a major inactive metabolite, which has only minimal antifungal activity. Other metabolites also formed such as hydroxyl voriconazole and dihydroxy-voriconazole. Voriconazole shows first pass by enzymes present in enterocytes as well as hepatocytes and major systemic metabolisms occur by cytochrome-P450 enzymes such as CYP2C19, CYP2C9, CYP3A4, CYP3A5, and the 25% metabolism occurs by Flavin containing mono-oxygenase FMO-1 and FMO-3. Renal and Biliary excretion of voriconazole (metabolized form) is about 75%-80% and 20%-25% respectively, whereas, the remaining 2% is excreted in urine as unchanged form. Voriconazole is a potent inhibitor of CYP2C19, CYP2C9, CYP2B6, and CYP3A4 enzymes, present in hepatocytes as well as enterocytes. Voriconazole is a p-glycoprotein (ABCB1) substrate at different levels (intestinal, hepatic, and renal levels) and also it is a weak inhibitor of this transporter. Being a lipophilic drug, Voriconazole would be in the un-ionized form as the pH of the formulation shifts towards a neutral value resulting in enhanced permeation **(Mohanty et al., 2013, Vanhove et al., 2017, Mikus et al., 2011, Herbrecht, 2004)**.

Clarithromycin (6-O-Methylerthromycin) is a semi-synthetic macrolide antibacterial agent with a 14-membered ring. The oral bioavailability of clarithromycin parent drug is 52-53% and terminal elimination half-life ($t_{1/2}$) is 8hr **(Logan et al., 1994)**. The usually recommended dose in adults of Clarithromycin is 250mg-500mg (P/O) twice a day for 7-14 days in various conditions and in some conditions are also given a single dose of 1000mg. About 53% of a single dose of clarithromycin is excreted in the urine and 40% in feces. The volume of distribution of clarithromycin is estimated to be 191 to 309L and plasma protein binding ranges from 42-72%. Clarithromycin is extensively metabolized by hepatic CYP3A4 and

forms a 14-R-hydroxyclarithromycin active metabolite and inactive metabolite N-desmethyl-clarithromycin **(Rodvold, 1999)**. Clarithromycin is an intense inhibitor of CYP3A4 and has the average inhibitory activity of CYP2C19, CYP2D6, and CYP1A2 enzymes at hepatic as well as the intestinal levels **(Furuta et al., 1999, Michalets, 1998)**.

At different levels (intestinal, hepatic, and renal levels), several transporters (ABCB1, ABCC2, OATP2B1, and OATP1A2)are substrates of clarithromycin **(Müller and Fromm, 2011)**. Voriconazole is an inhibitor of several transporters like breast cancer resistance protein (BCRP), p-glycoprotein, multidrug resistance-associated protein (MRP-1, MRP-2, MRP-4, and MRP-5), and bile salt export pump (BSEP), but exhibited an inhibitory activity of less than 60% **(Lempers et al., 2016, Mikus et al., 2011)**. Clarithromycin is also an inhibitor of p-glycoprotein at enterocytes (luminal), hepatocytes (canalicular), and renal (luminal) sites as well as an inhibitor of OATP1B1 and OATP1B3 at hepatocytes (sinusoidal) and intestinal level **(Müller and Fromm, 2011)**. Strong inhibitory (Ic_{50}) activity of OATP4C1 has also been observed by clarithromycin at intestinal and renal sites **(Sato et al., 2017)**. Clarithromycin is a potent inhibitor of the taurocholate uptake in rat OATP1A5-transfected Madin-Darby canine kidney cells, the nearest analog to human OATP1A2 **(Garver et al., 2008)**. According to the BCS classification, voriconazole and clarithromycin both are class-II drugs **(Kumar et al., 2014, Kristin et al., 2017)**. Nature and pKa of both interacting drugs (i.e., clarithromycin weakly basic in nature with 8.76 pKa and voriz exhibiting both sets of pKa values i.e., basic: 1.76 pKa as well as acidic pKa values: 4.36 and 12.7) make these drugs better candidates for possible potential PK-DDIs.

Keeping in view the nature of voriconazole and clarithromycin a pharmacokinetic drug-drug interaction may likely be possible.

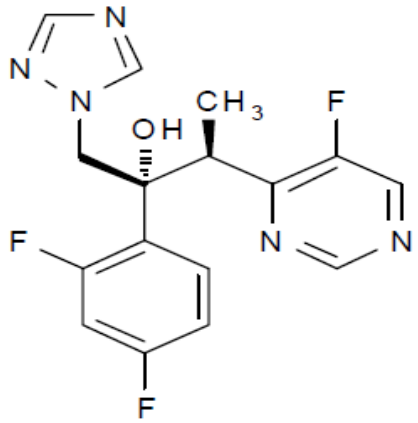

Fig.1: Chemical structure of voriconazole

2. OBJECTIVES

The main objectives of this study will be

1. To develop a sophisticated, robust, and sensitive quantification method using HPLC for the determination of voriconazole in biological fluids.
2. To measure the pharmacokinetic parameters [i.e., C_{max}, T_{max}, $T_{1/2}$, AUC, etc.] of voriconazole in healthy volunteers of Pakistan.
3. To evaluate the PK-DDI of voriconazole with clarithromycin and to study the impact of clarithromycin co-administration on the pharmacokinetic parameters of voriconazole.
4. To interpret the data statistically.

3. LITERATURE REVIEW

Co-administration of a precipitant drug with an object drug may alter the object drug's response in the patient. Some drug interactions are clinically significant and beneficial, so it is desirable to use their simultaneous administration for better therapeutic response and reduced potential ADRs. The majority of drug interactions are not clinically significant and may be detrimental resulting in adverse events. Voriconazole's drug interactions can be categorized into: contraindicated, needing dose adjustment, monitoring levels, and no adjustment required **(Herbrecht, 2004)**. Many DDI of voriconazole is well documented in the

literature. Purkins and his co-workers performed an open-label, randomized, and cross-over study on 12 healthy volunteers. Effect of cimetidine on pharmacokinetic parameters of voriconazole has been evaluated and an insignificant increase in AUC and C_{max} of voriconazole has been observed, so only monitoring the voriconazole concentration in the body in long term use for toxicity is sufficient (**Purkins et al., 2003b).** Another study is conducted on voriconazole and ritonavir, in which a serious DDI has been reported. C_{max} of voriconazole is decreased by 150% because ritonavir is (CYP2C19 and CYP2C9) enzyme inducer, so an alternative therapy or contraindication along with ritonavir (400mg BID) has been suggested **(Liu et al., 2007)**.

Drug interaction of voriconazole with phenytoin has also been reported in the literature. The AUC and C_{max} of voriconazole decreased by150% because phenytoin is a (CYP2C19 and CYP2C9) enzymes inducer so increased maintenance dose and TDM of voriconazole have been recommended **(Purkins et al., 2003a).** Andrew and his fellow researchers have performed a DDI study of voriconazole with ethinyloestradiol and norethindrone. This study reported increased AUC and C_{max} of voriconazole by 100% because ethinyloestradiol is a CYP2C19 enzyme inhibitor. They have reported that this one is significant interaction and concurrent use of voriconazole, ethinyloestradiol, and norethindrone medications are well-tolerated **(Andrews et al., 2008).** The effect of efavirenz on voriconazole pharmacokinetics has also been studied. This study reported a decrease in AUC by150% because efavirenz is CYP2C19 and CYP2C9 enzymes inducer **(Damle et al., 2008)**.

In recent research conducted on voriconazole with flucloxacillin co-administration in patients having chronic granulomatous disease and influenza-associated aspergillosis, a decrease in plasma voriconazole concentration has been reported. Flucloxacillin induced CYP3A4 enzyme resulting in decreased Cmax. In this study, the researchers have suggested close monitoring of plasma concentration of voriconazole and avoidance of the combination if possible (**Muilwijk et al., 2017).**

A case study of pulmonary aspergillosis patients reported a decrease in voriconazole plasma concentration by co-administration with darunavir (non-

peptidic HIV protease inhibitor). This study report suggested that voriconazole, ritonavir, and darunavir should be given cautiously or combination is avoided **(Becker et al., 2015).**

Many DDIs occur because voriconazole has variable and non-linear pharmacokinetic behavior. Voriconazole is a CYP2C19 and CYP3A4 enzymes inhibitor as well as a substrate of these enzymes. Enzyme CYP2C19 has genetic polymorphism: poor, moderate, and extensive metabolizers **(Bahar et al., 2017)**. Asian peoples are mostly poor CYP2C19 metabolizers so DDI may be possible in this region and voriconazole may show variable C_{max} because of non-linearity **(Mikus et al., 2011)**. Clarithromycin is CYP3A4 and CYP2C19 enzymes inhibitor and voriconazole are also a substrate and inhibitor of these two enzymes **(Furuta et al., 1999).** Both drugs share the same enzyme pathway so DDI may be possible. To our knowledge, no work has been done for the evaluation of the effect of clarithromycin on pharmacokinetic parameters of voriconazole to date.

4. METHODOLOGY

This study will be designed in the following three steps.

Step-1: Development of Quantification Method and Its Validation

In the first phase of the current study, we will develop an HPLC method and validation according to standard guidelines for the quantification of voriconazole in a biological matrix. The first phase of the study will comprise of development and validation of the HPLC method for the identification as well as determination of voriconazole in biological fluids.

Step-2: Evaluation of Pharmacokinetic Drug-Drug Interaction

During the second step, sample collection will be carried out and blood samples will be collected in EDTA or heparinized tubes from the enrolled human volunteers, administered with voriconazole alone or co-administered with clarithromycin at specified periods. Further processing of the sample will be done for extractions and subsequent analysis with the developed analytical method. Evaluation of possible pharmacokinetic drug-drug interaction will be carried out through a comparison of pharmacokinetic parameters.

Study Design and Subject

A study designed for drug interaction will be a single oral dose, open-label, randomized, cross-over study of healthy volunteers. The ethical approval of the protocol will be taken from the local ethical committee of the Pharmacy department, Abdul Wali Khan University, Mardan before initiation. This study will follow the "*ethical principles of the Helsinki declaration for medical research involving human subjects"* and "*good clinical practice guidelines*". Written consent will be obtained from all included volunteers in the DDI study. The study will be comprised of two treatment sequences with a two-week washout period i.e., given in Table-I;

Sequence	**Treatment-1** **Group-I** **(n= 12)**	**Treatment-2** **Group- II** **(n = 12)**
Sequence-1	Voriconazole alone (Vfend® Oral Two Tab, strength of 200mg)	Voriconazole + clarithromycin (Vfend® Oral Two Tab, Strength of 200mg with klaricid® Oral Tab, Strength of 500mg)
Two Week Washout Period		
	Treatment-2	**Treatment-1**
Sequence-2	Voriconazole + clarithromycin (Vfend® Oral sTwo Tab, strength of 200mg with klaricid® Oral Tab, Strength of 500mg)	Voriconazole alone (Vfend® Oral Two Tab, Strength of 200mg)

Table-1: Two Treatment Sequence, Open Labeled, Cross-Over Study Design for the Pharmacokinetic DDI-Study of Voriconazole with Clarithromycin

Inclusion Criteria

Male Pakistani volunteers in good health aged 18-35 years will be enrolled as participants in this study. The selection will be based on: a complete detailed medical

history, clinical examination, voriconazole hypersensitivity test, and evaluation of various biochemical tests like Blood Glucose Level, Hemoglobin (Hb) Level, Serum Glutamic-Pyruvic Transaminase (SGPT) Or Alanine Amino Transferase and Aspartate (ALT and AST, respectively) Level, Urine Test, BUN Level, Albumin to Creatinine Ratio (ACR) Test, Glomerular Filtration Rate (GFR) Level, etc.

Exclusion Criteria

Those volunteers who have a history of voriconazole hypersensitivity reaction, deviation from normal values in the biochemical test report, having any pathology like chronic renal disease, hepatic impairment, and having any cardiovascular, gastrointestinal tract, hematopoietic disorders will be excluded from the study. Alcohol addicted, smokers and volunteers who cannot sign the permission consent form will be excluded from the study.

Collection of Blood-Samples

Blood samples (approximately 3cc) will be collected from overnight fasting inducted volunteers in heparinized tubes at specific time intervals of 0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12 and 24 hours after administration of two tablets of voriconazole (200mg) either alone or co-administration with clarithromycin (500mg). After taking blood samples, immediately these samples will be centrifuged to separate plasma from blood (RBC) and will be stored at -80^0C until analysis.

Samples Analysis

We will develop an RP-HPLC/UV-Vis method for the measurement of voriconazole concentration in biological fluid. The stored samples will be brought back to room temperature by thawing technique and the drug will be extracted from plasma samples with already established extraction solvents and subsequently analyzed with the developed method.

Step-3: Data Assessment and Analysis

In this phase, pharmacokinetic parameters used for PK-DDI assessment will be analyzed statistically using compartment and/or non-compartmental approaches. Assorted pharmacokinetic parameters like C_{max} (µg/ml), T_{max} (hrs), $T_{1/2}$ (hrs), $[AUC]_{0-t}$ (µg.h/ml), AUMC (µg.h/ml), MRT (hrs), and V_d (L) will be determined

from plasma drug concentration Vs. time profile. All pharmacokinetic parameters will be evaluated using different pharmacokinetic software like PK-Summit® etc., and for graphical data analysis MS-Excel, Minitab, etc. will be used. Appropriate statistical tests like t-test and analysis of variance (ANOVA) will be performed and data will be presented graphically.

5. TENTATIVE TIME

Literature Survey: one month

Research: 06 month

Thesis writing: 06 month

6. REFERENCE

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Title: Pharmacokinetic Drug-Drug Interaction Study of Voriconazole with Clarithromycin

ASRB Approval Date of Study and Study-Title: September 28 2018

CONSENT FORM

PHARMACOKINETIC DRUG-DRUG INTERACTION STUDY OF VORICONAZOLE WITH CLARITHROMYCIN

Name of the participant: _____
Name of the principal (Co-) Investigator: _____
Name of the institution: _____

Documentation of the informed consent
I, _____, have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in
"_____" (title of study)

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been advised about the risks associated with my participation in the study.
5. I have informed the investigator of all the treatments I am taking or have taken in the past_____ months including any desi (alternative) treatments.
6. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
7. I have not participated in any research study within past _____ month(s).
8. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.
9. I hereby give permission to the investigator to release the information obtained from me as a result of participation in this study to the sponsors, regulatory authorities, government agencies, and ethics committee. I understand that they may inspect any original records.
10. My identity will be kept confidential if my data are publicly presented.
11. I have had my questions answered to my satisfaction.
12. I have decided to be in the research study.

Participant's initials:
Name and signature / thumb impression of the participant
Name: _____ Signature: _____ Date: _____ Time: _____
Address and contact number of the impartial witness: _____
_____
Name and signature of the investigator or his representative obtaining consent:
Name: _____ Signature: _____ Date: _____

Investigator certificate
I certify that all the elements including the nature, purpose and possible risks of the above study as described in this consent document have been fully explained to the subject. In my judgment, the participant possesses the legal capacity to give the informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate,
Signature of the investigator: _____ Date: _____
Name of investigator: