PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF VORICONAZOLE FOR INVASIVE ASPERGILLOSIS TREATMENT IN THAI ADULT PATIENTS

Miss Montira Tantasawat

A Dissertation Submitted in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy Program in Pharmaceutical Care

Department of Pharmacy Practice

Faculty of Pharmaceutical Sciences

Chulalongkorn University

Academic Year 2016

การศึกษาเภสัชจลนศาสตร์/เภสัชพลศาสตร์ของวอริโคนาโซลสำหรับรักษาการติดเชื้อแอสเปอร์จิลลัสชนิดรุกรานในผู้ป่วยผู้ใหญ่ชาวไทย

นางสาวมณฑิรา ตันตสวัสดิ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรดุษฎีบัณฑิต
สาขาวิชาการบริบาลทางเภสัชกรรม ภาควิชาเภสัชกรรมปฏิบัติ
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2559

Thesis Title	PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF VORICONAZOLE FOR INVASIVE ASPERGILLOSIS TREATMENT IN THAI ADULT PATIENTS
By	Miss Montira Tantasawat
Field of Study	Pharmaceutical Care
Thesis Advisor	Assistant Professor Chankit Puttilerpong, Ph.D.
Thesis Co-Advisor	Associate Professor Duangchit Panomvana Na Ayudhya, Ph.D. Prawat Chantharit, M.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Doctoral Degree

.....Dean of the Faculty of Pharmaceutical Sciences

(Assistant Professor Rungpetch Sakulbumrungsil, Ph.D.)

THESIS COMMITTEE

.....Chairman

(Associate Professor Thitima Pengsuparp, Ph.D.)

.....Thesis Advisor

(Assistant Professor Chankit Puttilerpong, Ph.D.)

.....Thesis Co-Advisor

(Associate Professor Duangchit Panomvana Na Ayudhya, Ph.D.)

.....Thesis Co-Advisor

(Prawat Chantharit, M.D.)

.....Examiner

(Thitima Wattanavijitkul, Ph.D.)

.....Examiner

(Nutthada Areepium, Ph.D.)

.....External Examiner

(Associate Professor Chonlaphat Sukasem, Ph.D.)

มณฑิรา ตันตสวัสดิ์ : การศึกษาเภสัชจลนศาสตร์/เภสัชพลศาสตร์ของวอริโคนาโซลสำหรับรักษาการติดเชื้อแอสเปอร์จิลลัสชนิดรุกรานในผู้ป่วยผู้ใหญ่ชาวไทย (PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF VORICONAZOLE FOR INVASIVE ASPERGILLOSIS TREATMENT IN THAI ADULT PATIENTS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ภก. ดร.ชาญกิจ พุฒิเลอพงศ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: รศ. ภญ. ดร.ดวงจิตต์ พนมวัน ณ อยุธยา , อ. นพ. ประวัฒน์ จันทฤทธิ์, 116 หน้า.

วอริโคนาโซลเป็นยาต้านเชื้อรากลุ่มเอโซลซึ่งมีเภสัชจลนศาสตร์แบบไม่เป็นเส้นตรงเนื่องจากเกิดการอิ่มตัวของเมทาบอลิสม และมีหลายปัจจัยที่มีผลต่อเภสัชจลนศาสตร์ของยา ปัจจุบันยังไม่มีการศึกษาถึงค่าทางเภสัชจลนศาสตร์ของวอริโคนาโซลในผู้ป่วยผู้ใหญ่ชาวไทยจึงไม่สามารถทำนายระดับยาวอริโคนาโซลได้อย่างแม่นยำ การศึกษานี้จึงมีวัตถุประสงค์เพื่อหาค่าทางเภสัชจลนศาสตร์ของวอริโคนาโซลในผู้ป่วยผู้ใหญ่ชาวไทย ปัจจัยที่มีผลต่อพารามิเตอร์ดังกล่าว รวมถึงหาความสัมพันธ์ระหว่างระดับยาวอริโคนาโซลกับผลทางคลินิกในการรักษาการติดเชื้อแอสเปอร์จิลลัสชนิดรุกราน โดยเก็บข้อมูลผู้ป่วยย้อนหลังจากการทบทวนเวชระเบียน ณ โรงพยาบาลรามาธิบดี ตั้งแต่ มกราคม พ.ศ. 2556 ถึง มีนาคม พ.ศ. 2559

มีผู้ป่วยจำนวน 53 รายที่สามารถคำนวณพารามิเตอร์ทางเภสัชจลนศาสตร์ของวอริโคนาโซลได้ ค่ามัธยฐานของ K_m ของวอริโคนาโซลเท่ากับ 0.26 มิลลิกรัมต่อลิตรและ 0.67 มิลลิกรัมต่อลิตรในผู้ป่วยที่มีการทำงานของ CYP 2C19 ปกติและต่ำกว่าปกติตามลำดับ ($p = 0.008$) ในขณะที่ค่ามัธยฐานของ V_{max} ของวอริโคนาโซลในผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกัน (0.43 และ 0.48 มิลลิกรัมต่อกิโลกรัมค่อชั่วโมงสำหรับผู้ป่วยที่มีการทำงานของ CYP 2C19 ปกติและต่ำกว่าปกติตามลำดับ) นอกจากฟีโนไทป์ของ CYP2C19 แล้วปัจจัยที่มีผลต่อค่า K_m คือ อายุ ระดับบิลิรูบินและแอลคาไลน์ฟอสฟาเทสในเลือด ในขณะที่ไม่มีปัจจัยใดของผู้ป่วยที่ทำนายค่า V_{max} ได้ เมื่อประเมินความสัมพันธ์ของระดับยาวอริโคนาโซลกับผลทางคลินิกในผู้ป่วยจำนวน 81 ราย พบว่าอัตราความสำเร็จในการรักษาคิดเป็นร้อยละ 76.5 ในขณะที่อัตราการเกิดพิษต่อตับจากยาคิดเป็นร้อยละ 13.6 เมื่อระดับยาวอริโคนาโซลต่ำสุดมีค่า 3-4 มิลลิกรัมค่อลิตร อัตราความสำเร็จในการรักษาจะสูงกว่าร้อยละ 90 และเมื่อระดับยาวอริโคนาโซลต่ำสุดมีค่าสูงกว่า 5 มิลลิกรัมต่อลิตร อัตราการเกิดพิษต่อตับจากยาจะเพิ่มสูงขึ้นอย่างชัดเจนเมื่อเปรียบเทียบกับระดับยาที่ต่ำกว่า

การศึกษานี้ให้ค่า K_m และ V_{max} ของยาวอริโคนาโซลในผู้ป่วยผู้ใหญ่ชาวไทย ซึ่งยังมีช่วงที่กว้าง แสดงให้เห็นถึงความแปรปรวนระหว่างบุคคลที่สูง ดังนั้นการเริ่มการรักษาตามขนาดยาที่แนะนำและทำการติดตามระดับยาในเลือดจึงมีความสมเหตุสมผล ระดับยาวอริโคนาโซลต่ำสุดที่แนะนำสำหรับการรักษาการติดเชื้อแอสเปอร์จิลลัสชนิดรุกรานในผู้ป่วยผู้ใหญ่ชาวไทยคือ 3-4 มิลลิกรัมต่อลิตร เนื่องจากให้อัตราความสำเร็จในการรักษาที่สูงและสามารถหลีกเลี่ยงการเกิดพิษต่อตับจากยาได้

ภาควิชา เภสัชกรรมปฏิบัติ ลายมือชื่อนิสิต .....

สาขาวิชา การบริบาลทางเภสัชกรรม ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ปีการศึกษา 2559 ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5476551833 : MAJOR PHARMACEUTICAL CARE

KEYWORDS: VORICONAZOLE / NONLINEAR PHARMACOKINETIC / INVASIVE ASPERGILLOSIS / CLINICAL OUTCOME / HEPATOTOXICITY / CYP2C19

MONTIRA TANTASAWAT: PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF VORICONAZOLE FOR INVASIVE ASPERGILLOSIS TREATMENT IN THAI ADULT PATIENTS. ADVISOR: ASST. PROF. CHANKIT PUTTILERPONG, Ph.D., CO-ADVISOR: ASSOC. PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D., PRAWAT CHANTHARIT, M.D., 116 pp.

An azole antifungal , voriconazole (VRZ), exhibits nonlinear pharmacokinetics (PK) due to saturated metabolism and several factors influence its PK. Currently, PK parameters of VRZ in adult Thai patients have not been identified, which causes uncertainty in VRZ level estimation. This study aimed to determine the VRZ PK parameters for adult Thai patients, factors influencing these parameters and the association between the VRZ concentration and clinical outcome in invasive aspergillosis (IA) treatment. Medical records of eligible patients at Ramathibodi Hospital during January 2013 and March 2016 were retrospectively reviewed.

Of all 53 patients including in pharmacokinetic study, the median K_m of were 0.26 mg/L and 0.67 mg/L for CYP2C19 EM and non-EM, respectively (p = 0.008). The V_{max} of voriconazole were not different between each CYP2C19 phenotype (0.43 vs. 0.48 mg/kg/h for CYP2C19 EM and non-EM, respectively). Other than CYP2C19 phenotype, age, TB, and ALP were the significant factors influencing the K_m, while none of patient's factors could predict V_{max}. Among eighty-one patients who were eligible for clinical outcome assessment, overall treatment success rate was 76.5 % and hepatotoxicity rate was 13.6%. The treatment success rate at VRZ C_{tr} of 3-4 mg/L was more than 90%. When compare to lower C_{tr} level, the hepatotoxicity rate was dramatically increased with VRZ C_{tr} of more than 5 mg/L.

This study provided K_m and V_{max} of VRZ for Thai adult patients with IA, however their wide range indicated the high variability between individuals. Therefore, the need to start VRZ treatment with the recommended doses followed by therapeutic drug monitoring was warranted. Recommended VRZ C_{tr} for IA treatment for Thai adult patients was 3-4 mg/L because of its high treatment success rate together with avoiding drug-induced hepatotoxicity.

Department:	Pharmacy Practice	Student's Signature	.....
Field of Study:	Pharmaceutical Care	Advisor's Signature	.....
Academic Year:	2016	Co-Advisor's Signature	.....
		Co-Advisor's Signature	.....

ACKNOWLEDGEMENTS

This thesis was successfully achieved through the cooperation of many individuals. First, I would like to express my sincere gratitude to my advisor, Dr.Chankit Puttilerpong for his advice and support given throughout my time in graduate school.

I am also indebted to my co-advisor, Dr.Duangchit Panomvanna Na Ayudhya for her advice, creative guidance, encouragement, valuable comments and mental support.

I would like to express my infinite thanks to my co-advisor, Dr.Prawat Chantharit for his kind assistannce and everlasting support.

I also wish to express my deep appreciation to all members of the thesis committee for spending their times to be on my thesis committee and for their suggestion and comments.

I would like to express my deep gratitude to all the patients who participated in this study, and the physicians and staffs at Ramathibodi Hospital for their support.

I also wish to express my deep appreciation to National Science and Technology Development Agency (NSTDA), Thailand for my graduate school and thesis funding.

I would like to express my infinite thanks to staffs in the Department of Pharmacy Practice for their assistance. I am really thankful to my classmates and friends for their friendship, consultation, guidance, suggestion, and kindness.

Finally, I would like to express my deep gratitude and appreciation to my family for their assistance, care cheerfulness, endless love and encouragement.

CONTENTS

Page

Page

Page

LISTS OF TABLES

LISTS OF ABBREVIATIONS

ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
Bili	Bilirubin
C	Concentration
CI	Confidence interval
Cl_{Cr}	Creatinine clearance
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P 450
d	day
DB	Direct bilirubin
DILI	Drug-induced liver injury
EM	Extensive metabolizer
F	Female
GGT	γ-glutamyl transpeptidase
h	Hour

Hb	Haemoglobin
Hct	Haematocrit
HIV	Human immunodeficiency virus
HUM	Heterozygous ultrarapid metabolizer
IA	Invasive aspergillosis
IM	Intermediate metabolizer
IQR	Interquatile range
IV	Intravenous
kg	Kilogram
L	Litre
LFTs	Liver function tests
M	Male
MIC	Minimum inhibitory concentration
mg	Milligram
MKD	Milligram per kilogram per day
N	Neutrophil
OR	Odds ratio
Plt	Platelet
PM	Poor metabolizer
SBECD	Sulfobutylether-beta-cyclodextrin

SCr	Serum creatinine
SS	Steady state
TB	Total bilirubin
TDM	Therapeutic drug monitoring
TTT	Time to toxicity
$t_{90\%}$	Time to reach 90% of steady state
ULN	Upper limit of normal
UM	Ultraraoid metabolizer
VRZ	Voriconazole
WBC	White blood cell
y	Year
µg	Microgram

CHAPTER I

INTRODUCTION

The antifungal agent voriconazole (VRZ) is a synthetic broad-spectrum triazole that is derived from fluconazole, and is recommended for the treatment of invasive fungal infections (IFIs) caused by common pathogens, such as *Aspergillus, Candida* and *Cryptococcus neoformans*, as well as less common pathogens, such as *Fusarium* and *Pseudallescheria* . Without treatment, IFIs are an important cause of mortality and morbidity, especially in immunocompromised patients, such as those receiving chemotherapy or immunosuppressive therapy (e.g., solid organ or bone marrow transplant patients, systemic lupus erythematous (SLE) patients), or those infected with human immunodeficiency virus (HIV). The pharmacokinetics of VRZ is non-linear and exhibits high inter- and intra-individual variability because it has saturated hepatic metabolism as well as different patient characteristics. The catabolism of VRZ is mainly mediated by CYP*2C19*, but also to a lesser extent by CYP*3A4* and CYP*2C9*. Thus, CYP*2C19* polymorphisms may explain some of the inter-individual variability in VRZ exposure. Many studies have shown that the frequency of *CYP2C19* polymorphisms varies among different ethnic groups. In addition to CYP2C19 polymorphism, various other factors, such as the patient's age, liver diseases, drug interactions, albumin level, C-reactive protein level, and body weight have been identified as influencing factors on VRZ plasma concentrations. Meanwhile, some studies have reported no significant relationship between the VRZ plasma concentrations and genotype, age, sex, or use of concomitant proton pump inhibitors. Consequentially, the inability to predict the VRZ plasma concentrations complicates its usefulness in clinical practice.

Pharmacodynamic studies using time-kill curve and murine candidiasis model suggested an exposure-response relationship. In clinical practice, the association between a low VRZ concentration and poor clinical outcome has been reported, but this

relationship is still equivocal and inconsistent. Some clinical studies have not found an association between the treatment outcome and VRZ drug level. Other than the VRZ concentration, many other factors influence the treatment outcome, including the patient's immune status and age, co-morbidities and removal of infected tissue. Adverse effects associated with VRZ include hepatotoxicity or elevated serum levels of hepatic enzymes, neurotoxicity, which may present with hallucination or visual disturbance, and rash. Disagreement on the relationship between the adverse events and VRZ concentration has also been reported.

Therefore, we performed this study to identify correlation between the factors (*CYP2C19* polymorphism, drug-drug interactions, patient's demographic data, etc.) and voriconazole pharmacokinetic (PK) parameters and develop the model to predict pharmacokinetic parameters (K_m, V_{max}) of voriconazole in Thai adult patients and to identify association between pharmacokinetic parameters (C_{tr}) and clinical outcome.

This study would provide pharmacokinetic parameters of voriconazole for Thai adult patients that will further be used in exploration of exposure-response relationship, therapeutic drug monitoring, and dosage adjustment for individual patients. In addition, the optimal dosage regimen of voriconazole for invasive aspergillosis treatment for Thai adult patient would be determined in order to maximize efficacy together with minimize toxicity.

CHAPTER II

LITERATURE REVIEW

1. Invasive fungal diseases (IFD)

Invasive fungal diseases (IFD) are associated with significant morbidity and mortality in immunocompromised or other high-risk patients, including patients with hematologic or other malignancies, and hematologic stem-cell transplant (HSCT) or solid-organ transplant (SOT) recipients receiving immunosuppressive therapy (1). The most common IFD are invasive candidiasis (IC) and invasive aspergillosis (IA). IFD is categorized into three subgroups; proven, probable, and possible diseases based on host factors, clinical, mycobiological, and radiological findings (2). Diagnosis of IFD by blood culture is almost always negative, the nonculture diagnostic approaches have been developed such as assay of 1,3-β-D glucan for detection of IC and IA, galactomannan for detection of IA, and PCR-based assays for detection of *Aspergillus* spp. DNA (3).

1.1 Antifungal therapy for IFD

Although the antifungal options are increase, the treatment outcomes are still unsatisfactory with mortality rates often more than 50%, depending on the pathogen and disease (4). Currently available antifungal agents approved for invasive fungal disease treatment and prophylaxis are polyenes (amphotericin B), triazoles (fluconazole, itraconazole, voriconazole, and posaconazole), echinocandins (caspofungin, micafungin, and anidulafungin), and flucytosine. These agents differ in mechanism of action, spectrum of pathogen coverage, pharmacokinetic/pharmacodynamic properties, indications, adverse drug reactions,

cost, and convenience to use. Among of them, triazole antifungals are available in both oral and injectable form while the others are available only the injection. Furthermore, triazole antifungals are generally well tolerated when compare to amphotericin B (5). These support the widely use of triazole antifungals.

Fluconazole and itraconazole are the first-generation triazole antifungals which still have roles in current routine clinical practice including prophylaxis, empirical therapy, and treatment of both superficial and invasive yeast infection for fluconazole and treatment of fungal skin and nail infections, dematiceous fungi and endemic mycoses such as coccidiodomycosis, histoplasmosis, blastomycosis, and sporotrichosis for itraconazole (6). Voriconazole and posaconazole are the new- or second-generation triazole antifungals which have broader spectrum of activity. At the present time, voriconazole is prominent and extensively used for many invasive fungal diseases treatment and prophylaxis especially in case of fluconazole or itraconazole is not an appropriate option. Voriconazole pharmacokinetics have large intra- and interindividual variability and its pharmacokinetic data in Thai patients remains limit, therefore, pharmacokinetic study of voriconazole in this population should be performed.

2. Voriconazole and its pharmacokinetic and pharmacodynamic profile

2.1 Voriconazole pharmacology and clinical use

Voriconazole is a synthetic derivative of fluconazole developed by substitution of the fluoropyrimidine ring for one of the azole group and an added α-methyl group lead to provide fungicidal activity against *Aspergillus spp.* and other molds (7). Voriconazole inhibits the cytochrome P-450 dependent enzyme 14-α-sterol demethylase as a result of disrupting the fungal membrane and halting fungal growth (8). Because of the potent activity against *Aspergillus spp.*, voriconazole is recommended as a primary therapy for many types of aspergillus diseases such as invasive pulmonary aspergillosis, invasive sinus aspergillosis, tracheobronchial

aspergillosis, and aspergillosis of the CNS (9). Besides invasive aspergillosis, voriconazole has been approved from US FDA for following indications: candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds; esophageal candidiasis; serious infections caused by *Scedosporium apiospermum* and *Fusarium spp.* including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy (10, 11).

Voriconazole is typically well tolerated, and its side effect profile is similar to other triazole antifungals with few differences (Table 1). In a study compare voriconazole and fluconazole in esophageal candidiasis treatment, more treatment-related adverse events were reported in voriconazole treated group (30%) than those receiving fluconazole (14%) (12). Gastrointestinal side effects were common (9%) and similar between voriconazole and fluconazole groups. However, the majority of patients experiencing a reported adverse reaction from voriconazole was abnormal vision (23%) that was transient, infusion related and without sequelae. This side effect of voriconazole is uncleared understood, and no pathologic retinal changes or long-term sequelae have been found (13). This effect typically occurs 30 minutes after infusion and recovers 30 minutes after onset. In a randomized, international, multi-center trial compared between IV voriconazole and liposomal amphotericin B as empirical therapy in febrile neutropenic patients, infusion related side effects were the most common adverse events attributed to voriconazole therapy, with 21.9% of patients described flashing lights (photopsia) or similar visual disturbance (14). Discontinuation of voriconazole therapy due to side effects was infrequent in these trials. Other well-known adverse reactions of voriconazole therapy include skin rash and transaminase elevation (15). There was a recommendation to monitor hepatic function at baseline and during voriconazole therapy. Similar to other triazole antifungals, prolong QTc interval has been reported in voriconazole therapy (16). Elevated serum trough voriconazole concentrations have been associated to the majority of side effects encountered in clinical practice, and higher levels (> 5.5 mg/l) although attributed with favorable outcomes, have

also been suggested responsible for the uncommon potential side effects of encephalopathy or hallucinations (17-19).

Table 1 Profile of common or important adverse effects of voriconazole (20)

Organ system	Description
Gastrointestinal disorders	Nausea, vomiting (< 5%)
	Abdominal pain (< 10%)
Skin and appendages	Pruritis, rash (< 10%)
	Potentially exfoliative
Liver and biliary system	Elevation of hepatic transaminases (< 15%),
	hepatitis (rare)
Kidney	-
Bone marrow	-
Immunologic	Anaphylaxis reported
Endocrine system	Adrenal insufficiency (rare)
Cardiovascular system	Potential to prolong QTc interval
Special senses	Altered/enhanced perception of light;
	photophobia, blurred vision (< 30%)
Nervous system	Hallucinations, confusion (10%), headache
Maximum tolerated dosage in clinical trials	800 mg/day (10 mg/(kg day)) have been
and limiting events for a period of 14 days	tolerated without dose-limiting events

2.2 Voriconazole pharmacokinetics

Voriconazole is available in both intravenous and oral formulations. As it has rapidly absorption within 2 hours and oral bioavailability of more than 90% allowing prompt to switch from intravenous-to-oral when clinically appropriate (8). After initiation of multiple administration of voriconazole, steady state plasma concentration will be achieved after approximately 5 days for both oral and intravenous dosing without a loading dose regimen. Oral or intravenous loading doses ensure that steady state plasma concentrations are attained within 24 hours (11, 21, 22). Oral absorption of voriconazole is reduced by food (11) but is not affected by gastric pH or by co-administration of oral ranitidine, cimetidine, or omeprazole (21). The volume of distribution of voriconazole is estimated to be 4.6

L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma voriconazole concentrations (21, 22). Multiple-dose studies showed nonlinear pharmacokinetics with maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve increasing disproportionately with increasing dose for both intravenous and oral formulations (23). It is likely due to saturation of voriconazole metabolism with respect to dose. The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole. Voriconazole is eliminated mostly via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine (21, 22). Pharmacokinetic parameters of VRZ were shown in Table 2 (20, 22).

2.3 Factors influence pharmacokinetics and pharmacodynamics of voriconazole

2.3.1 CYP2C19 polymorphisms

Voriconazole is both a substrate and an inhibitor of CYP2C19 (major), CYP2C9, and CYP3A4 enzymes (22, 23), relationships of voriconazole and various CYPs were shown in Table 3 (22). *In vivo* studies indicated that CYP2C19 was significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism with more than 30 allelic polymorphisms have been identified that were associated with decreased, increased, or unaltered enzymatic activity (24). About 15-20% of Asian populations may be expected to be poor metabolizers (PMs). For Caucasians and Blacks, the prevalence of poor metabolizers was 3-5% (21). In Thai population, there was a CYP2C19 polymorphism study collected data from 1,051 patients and 40.72% of the patients were predicted as extensive metabolizers (EM), 41.95% as intermediate metabolizers (IM), 13.03% as poor metabolizers (PM), and 4.30% as ultra-rapid metabolizers (UM) (25). Another study performed in 115 Thai patients reported the frequency of CYP2C19 phenotypes of

51.30% as EM, 36.52% as IM, and 12.18% as PM (26). The PM phenotype was caused by the *CYP2C19*2* (681G>A, splicing defect) and *CYP2C19**3 (636G>A, W212X, premature stop codon) polymorphisms. On the other hand, *CYP2C19*17* was reported to be associated with increased gene transcription linked to -806C>T causing ultra-rapid metabolism. However, the magnitude of this effect seems to be considerably smaller than that of the **2* and **3* alleles [23].

Table 2 Pharmacokinetic parameters of voriconazole in healthy volunteers and patients (20, 22)

Parameter	Value
Oral bioavailability (%)	>90
Food effect	Empty stomach
Plasma protein binding (%)	58
Volume of distribution (L/kg)	4.6
Penetration	
CSF (%)	60
Vitreal (%)	38
Urine (%)	< 2
Clearance (L/h/kg)	0.2–0.5
Peak plasma concentration (μg/mL)	
6 mg/kg IV q12h on day 1; maintenance dose 3 mg/kg q12h	3–4.7
400mg PO q12h on day 1; maintenance dose 200mg q12h	2–2.3
AUC_τ (μg • h/mL)[a]	
6 mg/kg IV q12h on day 1; maintenance dose 3 mg/kg q12h	13
400mg PO q12h on day 1; maintenance dose 200mg q12h	9–11
Elimination half-life (h)	6
Time to reach peak plasma concentration (h)	<2
Major routes of elimination	hepatic (CYP2C19; major, CYP3A4 and CYP2C9; minor) and renal (metabolites)

[a] AUC_τ values are calculated over a dosing interval of 12 hours.

AUC_τ = area under the plasma concentration-time curve during a dosage interval **τ**; **CSF** = cerebrospinal fluid; **IV** = intravenous; **PO** = orally; **q12h** = every 12 hours.

Table 3 Relationships of voriconazole and various cytochrome P450 (CYP) isoenzymes (22)

Variable	CYP3A4	CYP2C19	CYP2C9
Levels in human liver microsomes	+++	+	+
Genetic polymorphism	++	+++	++
Voriconazole induces	–	ND	ND
Voriconazole inhibits	++	++	+++
Voriconazole is substrate	++	+++	+

ND = not determined; **+** indicates low; **++** indicates medium; **+++** indicates high;

– indicates no.

Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers had, on average, 4-fold higher voriconazole exposure (AUC) than their homozygous extensive metabolizer counterparts. Subjects who were heterozygous extensive metabolizers had, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. However, currently, no dosage adjustments were recommended with regard to this observation (21). Lee S et. al. also reported the effect of CYP2C19 polymorphism on pharmacokinetic of voriconazole in 18 healthy volunteers. They found that bioavailability was not significantly different among the CYP2C19 genotypes. After a single intravenous or oral dose, voriconazole exposure in PMs was approximately 3 times higher when compared with EMs. At steady state, the plasma trough concentration (just before next dose) and area under the concentration-time curve for PMs were about 5 times and 3 times higher than EMs, respectively (27). In the patients, there were some studies demonstrared that patients with CYP2C19 PM had voriconazole trough concentration higher than EM (26, 28, 29) and IM (29). Dolton's group reported that among 240 patients receiving 200 mg of voriconazole twice daily, predicted trough concentrations on day 7 were < 2 mg/L for oral and intravenous regimens for 72% and 63% of patients without CYP2C19 loss-of-function (LoF) alleles, respectively, with 49% and 35% below this threshold with 300 mg twice daily dosing (30). Conversely, these regimens resulted in 29%, 39%, 57% and 77% of patients with CYP2C19 LoF alleles with voriconazole trough concentrations $\geq$ 5

mg/L. These results suggested that current dosing regimens of voriconazole resulting in subtherapeutic levels in many patients without CYP2C19 LoF alleles, suggesting the need for higher doses, whereas, these regimens resulting in supratherapeutic level in a high proportion of patients with reduced CYP2C19 activity. They also found that participants with one or more CYP2C19 LoF alleles had a 41.2% lower V_{max} for voriconazole (30). On the contrary, Hamadeh's group reported that compared with patients with the other phenotypes, heterozygous ultrarapid metabolizers (HUMs)/ ultrarapid metabolizers (UMs) had a lower steady-state trough level (4.26 ± 2.2 mg/L vs. 2.86 ± 2.3 mg/L, p = 0.0093) and a higher prevalence of subtherapeutic trough concentration (16% vs. 52%, P=0.0028), with an odds ratio of 5.6 (95% CI: 1.64–19.24, p = 0.0044) (31). These findings indicated that adults with the CYP2C19 HUM or UM phenotype were more likely to have subtherapeutic concentrations with weight-based voriconazole dosing (31). Table 4 showed the summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentrations.

Effects of CYP2C19 polymorphism on clinical outcome of voriconazole therapy still controversy. Meta-analysis of 10 studies involving 598 patients performed by Li's group found that PM phenotype was associated with a higher voriconazole treatment success rate compared with EM phenotype (risk ratio (RR), 1.31; 95 % CI, 1.04–1.67; P = 0.02) (28). However, there was no significant association between CYP2C19 polymorphisms and daily maintenance dose, overall adverse events, hepatotoxicity, and neurotoxicity (28). In the contrary, some studies reported the association between CYP2C19 polymorphism and voriconazole toxicity or adverse events. Sienkiewicz and coworker found that patients with at least one loss of function allele (*2) were more likely to experience adverse drug reactions than those, with different genotypes (32). In addition, Trubiano's group also reported that voriconazole exposure and toxicity was highest for IM and lowest for HUM/UM phenotypes (33).

Table 4 Summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentrations

Ref	Study design	Patient population	Intervention	Demonstrated CYP2C19–voriconazole concentration relationship	Conclusions
(34)		35 healthy drug-free individuals	Single VRZ 400-mg dose; genotyped for CYP2C19*2, *3, and *17	Yes	AUC differed significantly between CYP2C19 phenotype groups: 3 times greater in PMs vs EMs ($p<0.01$); CYP2C19 genotype accounts for 49% of VRZ's AUC variability after multiple regression analysis ($p<0.0001$)
(35)	Single-center randomized crossover trial	18 Chinese male volunteers	Crossover between placebo and erythromycin 500 mg 3 times/day for 4 days + VRZ 200 mg given 30 min after 10th erythromycin dose	Yes	Significant differences in t1/2, AUC0–24, and AUC0-∞ between PMs, IMs, and EMs ($p<0.05$), with PMs having the highest concentrations and longest half-life; authors recommended dosage reduction in PMs and IMs for VRZ monotherapy
(27)	Open-label single- and multiple-dose parallel-group study	18 healthy Korean male volunteers	VRZ 200 mg IV 91 dose, then a 1-wk washout followed by a VRZ 200-mg oral single dose, then 200 mg twice/day for 5 days	Yes	Mean AUC_{∞} of IMs and PMs after IV dose was 1.5 and 3.4 times higher than EMs, respectively ($p=0.002$); these findings exhibited similar differences after oral administration ($p=0.002$); mean troughs were 2.8 times higher in IMs than in EMs ($p=0.005$) and 5.1 times higher in PMs than in EMs ($p=0.008$)

Table 4. (cont.) Summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentration

Ref	Study design	Patient population	Intervention	Demonstrated CYP2C19–voriconazole concentration relationship	Conclusions
(36)	Retrospective analysis	37 Japanese pediatric patients	Patients received IV VRZ; genotyped for CYP2C19*2, *3, and *17	Yes	All patients with troughs >5 μg/ml (units corrected) were PMs or IMs; troughs were also higher in PMs and IMs compared with EMs and UMs (p=0.004); two UMs had very low concentrations (0.09 and 0.12 μg/ml (units corrected); VRZ plasma concentration in children is significantly correlated with CYP2C19 phenotype
(37)	Controlled open-label	20 unrelated healthy Han Chinese male volunteers	Single 200-mg oral dose of VRZ after being smoking, coffee, alcohol, and medication free for 1 wk	Yes	C_{max} in UMs was higher than in EMs (p=0.036) and PMs (p = 0.035); $t_{1/2}$ of UMs was 51% of $t_{1/2}$ of PMs (p = 0.002); UM $AUC_{0-\infty}$ was 48% and 85% lower than that of EMs (p = 0.001) and PMs (p < 0.001), respectively; significant differences in t1/2, AUC, CL/F values were noted among all three groups (EMs, PMs, and UMs)
(38)	Observational study	12 healthy Japanese subjects	VRZ 200 mg or 300 mg orally twice/day for 10 days	Yes	VRZ plasma concentration was 3 times higher in PMs than in EMs

Table 4. (cont.) Summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentration

Ref	Study design	Patient population	Intervention	Demonstrated CYP2C19–voriconazole concentration relationship	Conclusions
(39)	Randomized two-phase crossover study	14 healthy Chinese males: 7 Ms and 7 PMs	VRZ 200-mg single dose in control group; treatment group had ginkgo biloba 120 mg twice/day for 12 days	Yes	PMs had 4 times higher AUC and 4 times lower CL/F than EMs ($p<0.05$ for both); CYP2C19 determines pharmacokinetics of VRZ; gingko biloba (inhibitor of CYP2C19 and CYP3A4) did not significantly affect the pharmacokinetics of single-dose VRZ
(40)	Retrospective analysis	335 patients with 747 plasma or blood samples collected during routine TDM vs control group of 51 healthy nonsmoking subjects	Single dose of VRZ 400 mg IV or orally was administered to controls; plasma samples were analyzed from patients who received IV VRZ and had observed VRZ concentrations of ≤ 0.2 μg/ml during routine TDM; genotyped for CYP2C19*2, *3, and *17	Yes	TDM group with low VRZ concentrations had significantly higher frequency of UMs compared with the control group ($p = 0.01$)

Table 4. (cont.) Summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentration

Ref	Study design	Patient population	Intervention	Demonstrated CYP2C19–voriconazole concentration relationship	Conclusions
(41)	Single-center open-label two-period crossover study	20 healthy whites	Single doses of VRZ 400 mg orally and IV assigned in a randomized order; genotyped for CYP2C19*2 and *3	Yes	AUC in PMs was 3 times higher than in EMs and 2 times higher than in IMs regardless of route of administration; PMs had bioavailability of 94.4% vs 75.2% in EMs (p=NS); PMs had 3–4 times slower CL/F than EMs (p<0.05)
(42)	Retrospective exploratory study	24 white lung transplant recipients with cystic fibrosis who received VRZ therapy	Treatment and prophylactic doses of VRZ	Yes	Daily doses were significantly higher in *17 carriers (35% more; 14.1 3.9 mg/kg) and EMs (29.6% more; 13.6 ± 3.2 mg/kg) vs IMs (9.5 ± 1.7 mg/kg) (p<0.05); multivariate analysis revealed that CYP2C19 accounted for 38% of maintenance (steady state) dose variability; time to achieve therapeutic range was significantly longer in carriers of *2 and *17 compared with EMs (p=0.012); mean time to therapeutic range 7 ± 5 days (range 2–20 days); CYP2C19 polymorphisms accounted for 38% of maintenance dose variability according to multivariate analysis;

Table 4. (cont.) Summary of studies evaluating the association between CYP2C19 polymorphisms and voriconazole concentration

Ref	Study design	Patient population	Intervention	Demonstrated CYP2C19–voriconazole concentration relationship	Conclusions
					authors recommended CYP2C19 genotyping prior to VRZ therapy initiation to help determine initial dose to promptly achieve therapeutic plasma concentrations without out-of-range troughs

Adapted from Obeng AO et. al. (43)

CYP2C19 polymorphism tended to affect voriconazole dosage requirement. The study on the impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in 35 genotyped adult patients with invasive fungal infections reported that the mean voriconazole dosage required to achieve target concentration was significantly higher in *CYP2C19*17* carriers compared with *CYP2C19*1/*1* individuals ($P < 0.001$): 2.57 ± 0.25 mg/kg twice daily in *CYP2C19*1/*1* patients versus 3.94 ± 0.39 mg/kg and 6.75 ± 0.54 mg/kg in **1/*17* and **17/*17* patients, respectively (44). In addition, exposure to voriconazole correlated with the *CYP2C19*17* variant. Indices of exposure for *CYP2C19*2* carriers were in line with the functional effect of this polymorphism compared with *CYP2C19*1/*1* individuals, however, comparison of dosage required to achieve target concentration were not statistically different (44). Another study in 144 patients with a probable or proven IFD requiring voriconazole therapy found that PM patients could be safely and effectively treated with 200 mg twice daily orally or intravenously, while non-PM patients with 300 mg twice daily orally or 200 mg twice daily intravenously (29). A recent study by Teusink's group compared the standard dosing of voriconazole with

genotype-directed dosing. A pilot study in 25 individuals undergoing hematopoietic stem cell transplantation who received an initial dose of voriconazole of 5 mg/kg twice daily, regardless of CYP2C19 genotype was reported. Their doses were then adjusted until the levels were within the target therapeutic range of 1–5.5 mg/L. A subsequent study performed in 20 genotyped individuals for *CYP2C19 *2, *3,* and **17* before voriconazole administration, and adjusted the initial voriconazole dose based on their genotype and the predetermined dosing schematic was created based on the median doses for each genotype seen in the pilot study as follows: PMs received 5 mg/kg/dose every 12 h, IMs or unknown metabolizers received 6 mg/kg/dose every 12 h, and EMs or UMs received 7 mg/kg/dose every 12 h. No PMs were present and only one UM (**1/*17*) was present in the genotype-directed dosing arm (45). Doses were then adjusted, as in the pilot study, until they were within the target range. Comparison of the genotype-directed dosing arm with the standard dosing arm showed that patients in the genotype directed dosing arm took a median of 6.5 days to achieve the target therapeutic range, whereas, patients in the standard dosing arm took a median of 29 days, a statistically significant difference (45).

2.3.2 Drug interactions

As voriconazole is a substrate and inhibitor of CYP2C19, CYP3A4, and CYP2C9, multiple drug interactions are likely. The patient's current medications should be reviewed for potentially deleterious drug interactions. Many drugs are contraindicated for concomitant use with voriconazole including rifampin, rifabutin, carbamazepine, efavirenz, long-acting barbiturates, high-dose ritronavir (400 mg q 12 hours), and St. John's Wort because voriconazole plasma exposure were significantly reduced (46). A recent systematic review by Li's study in 2017, the influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole, found that the combination use of high-dose efavirenz, high-dose ritonavir, St John's wort, rifampin, phenobarbital, or carbamazepine with

voriconazole was contraindicated as instructed in the drug label (47). Low-dose efavirenz, low-dose ritonavir, rifabutin and phenytoin may be used together with voriconazole provided TDM and dose adjustment of voriconazole. Moreover, this study shows there is low risk of drug–drug interactions when voriconazole is co-administered with etravirine or *Gingko biloba*; however, whether the use of glucocorticoids has a clinically significant effect on voriconazole still requires more evidence (47).

The plasma exposure of these following drugs were significantly increased, so coadministration with voriconazole is contraindicated; sirolimus, rifabutin, efavirenz, quinidine, ergot alkaloids, and pimozide. Interactions between voriconazole and agents which were a substrate, inhibitor, or inducer of these three isozymes lead to frequent monitor for adverse events and toxicity together with efficacy of affecting drugs (11, 21, 22). The main drug interactions observed with voriconazole is shown in Table 5 (48).

Proton pump inhibitors (PPIs) are widely used medications that undergo CYP450-dependent metabolism by CYP2C19, CYP3A4 and CYP2C9, which makes these drugs competitive inhibitors of voriconazole. A recent study aimed to determine the influence of PPIs on the pharmacokinetics of voriconazole and to characterise potential drug–drug interactions (DDIs) between voriconazole and various PPIs (omeprazole, esomeprazole, lansoprazole and rabeprazole) were reported (49). Using adjusted physicochemical data and the pharmacokinetic (PK) parameters of voriconazole and PPIs, physiologically based pharmacokinetic (PBPK) models were built and were verified in healthy subjects using GastroPlus™ to predict the plasma concentration–time profiles of voriconazole and PPIs. These models were then used to assess potential DDIs for voriconazole when administered with PPIs. The results indicated the PBPK model-simulated plasma concentration–time profiles of both voriconazole and PPIs were consistent with the observed profiles. In addition, the DDI simulations suggested that the PK values of voriconazole increased to various degrees when combined with several PPIs. The

area under the plasma concentration–time curve for the time of the simulation (AUC_{0-t}) of voriconazole was increased by 39%, 18%, 12% and 1% when co-administered with omeprazole, esomeprazole, lansoprazole and rabeprazole, respectively. Omeprazole was the most potent CYP2C19 inhibitor tested, whereas rabeprazole had no influence on voriconazole (omeprazole > esomeprazole > lansoprazole > rabeprazole). However, in consideration of the therapeutic concentration range, dosage adjustment of voriconazole was unnecessary regardless of which PPI was co-administered (49). These results were concordant with Yasu's study which reported that lansoprazole had more effect on voriconazole level than rabeprazole (50). There was one prospective observational study perfomed in Thai patients to study the effect of PPIs on plasma voriconazole concentration in Thai Patients who had IFD (21). They found that of 54 patients enrolled, forty-one patients (87.2%) received PPIs, among which 37 (90.2%) were omeprazole. Patients with PPIs use had no difference in plasma voriconazole concentration, when compared with those without PPIs use, at day 3 (5.89 vs 5.44 mg/L, p = 0.744), day 7 (5.4 vs 5.29 mg/L, p = 0.471), day 14 (2.40 vs 3.13 mg/L, p = 0.372) and day 28 (1.77 vs 3.23 mg/L, p = 0.314). Although there was a trend toward higher plasma voriconazole concentration in patients receiving higher omeprazole dose (>20 mg/day), the difference between those treated with high (>20 mg/day) and low (20 mg/day) doses of omeprazole was not statistically significant at day 3 (6.27 vs 4.87 mg/L, p = 0.429), day 7 (7.44 vs 3.78 mg/L, p = 0.166), day 14 (2.52 vs 1.68 mg/L, p = 0.534) and day 28 (2.51 vs 1.44 mg/L, p = 0.154). Similarly, the duration of omeprazole use in concurrent with voriconazole treatment was not associated with plasma voriconazole concentration in infected patients (21).

2.3.3 Gender

In a multiple oral dose study, the mean C_{max} and AUC_{τ} for healthy young females were 83% and 13% higher, respectively, than in healthy young males (18-45 years), after tablet dosing. In the same study, no significant differences in the mean

C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C_{max} was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively. In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary (21).

Table 5 Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP3A4 substrates	Alfentanil	Voriconazole reduces alfentanil and fentanyl clearance and prolongs their half-life
	Alprazolam	Voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (risk for prolonged sedative effect)
	Astemizole	Concomitant use with voriconazole is contraindicated (risk for QT prolongation)
	Buspirone	Buspirone concentrations may be increased with concurrent voriconazole use
	Calcium channel blockers	Voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4
	Cisapride	Concomitant use with voriconazole is contraindicated (risk for QT prolongation)
	Contraceptives	Voriconazole increases Cmax and AUC of oral contraceptives by 36 and 61% (ethinyl estradiol), and 15 and 53% (norethindrone), respectively; voriconazole Cmax and AUC is also increased by 14 and 46%, respectively
	Cyclosporine	Voriconazole increases cyclosporine Cmax and AUC by 1.1 and 1.7 times, respectively (higher risk for nephrotoxicity)
	Delavirdine	The metabolism of voriconazole may be inhibited by delavirdine, which is also a CYP3A4 inhibitor and a CYP450 inducer

Table 5. (cont.) Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP3A4 substrates	Efavirenz	Concomitant use with voriconazole is contraindicated (two-way interaction). Efavirenz is also a CYP3A4 inhibitor and a CYP450 inducer
	Ergot alkaloids	Concomitant use with voriconazole is contraindicated (may lead to ergotism)
	HIV protease inhibitors	Voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g., saquinavir, amprenavir and nelfinavir, but not indinavir), and voriconazole metabolism may be inhibited by drugs such as saquinavir and amprenavir. These drugs are also CYP3A4 inhibitors
	Ibuprofen	Voriconazole increases the levels of exposure to ibuprofen by twofold. Ibuprofen is also a CYP3A4 inhibitor
	Indinavir	No significant drug interactions with voriconazole in healthy subjects. Indinavir is also a CYP3A4 inhibitor. For other HIV protease inhibitors, see above
	Lovastatin	Voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4 (higher risk for rhabdomyolysis)
	Methadone	Voriconazole increases Cmax and AUC of the pharmacologically active R-methadone by 31 and 47%, respectively (risk for QT prolongation). Methadone is also a substrate for CYP2C19 and CYP2C9
	Methylprednisolone	Voriconazole may increase exposure to steroids, including betamethasone, dexamethasone, hydrocortisone, fludrocortisone, budesonide and fluticasone. The effects on prednisolone are less pronounced (see below)

Table 5. (cont.) Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP3A4 substrates	Midazolam	Voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (risk for prolonged sedative effect)
	Nevirapine	The metabolism of voriconazole may be inhibited by nevirapine, which is also a CYP3A4 inhibitor and a CYP450 inducer
	Omeprazole	Omeprazole increases Cmax and AUC of voriconazole by 15 and 40%, respectively; voriconazole increases Cmax and AUC of omeprazole by twofold and fourfold, respectively. Omeprazole is also a CYP2C19 inhibitor and substrate
	Pimozide	Concomitant use with voriconazole is contraindicated (risk for QT prolongation)
	Prednisolone	Voriconazole increases Cmax and AUC of prednisolone by an average of 11 and 34%, respectively
	Quinidine	Concomitant use with voriconazole is contraindicated (risk for QT prolongation)
	Ritonavir	Co-administration of voriconazole and high-dose ritonavir (e.g., 400 mg b.i.d.) is contraindicated. Voriconazole is also best avoided with low-dose regimens of ritonavir (e.g., 100 mg b.i.d.). Ritonavir is also a CYP3A4 inhibitor and a potent CYP450 inducer
	Sildenafil	Voriconazole may potentially increase/prolong the pharmacologic effects of sildenafil (also vardenafil and tadalafil)
	Sirolimus	Voriconazole results in sirolimus Cmax and AUC increments by 7- and 11-fold, respectively. Co-prescription with voriconazole is not recommended (although a study reported a successful experience with co-administration based on TDM)

Table 5. (cont.) Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP3A4 substrates	Tacrolimus	Voriconazole increases tacrolimus Cmax and AUC by twofold and fourfold, respectively (higher risk for nephrotoxicity)
	Terfenadine	Concomitant use with voriconazole is contraindicated (risk for QT prolongation)
	Triazolam	Voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (risk for prolonged sedative effect)
	Vinblastine	Voriconazole may increase the plasma concentrations of the vinca alkaloids (higher risk for neurotoxicity)
	Vincristine	Voriconazole may increase the plasma concentrations of the vinca alkaloids (higher risk for neurotoxicity
CYP3A4 inhibitors	Delavirdine	See above. Delavirdine is also a CYP3A4 substrate and a CYP450 inducer
	Efavirenz	See above. Efavirenz is also a CYP3A4 substrate and a CYP450 inducer
	Everolimus	Voriconazole may increase the serum concentration of everolimus by 7.5-fold. Avoid combination
	HIV protease inhibitors	See above. These drugs are also CYP3A4 substrates
	Ibuprofen	See above. Ibuprofen is also a CYP3A4 substrate
	Indinavir	See above (no significant drug interactions with voriconazole in healthy subjects). Indinavir is also a CYP3A4 substrate
	Nevirapine	See above. Nevirapine is also a CYP3A4 substrate and a CYP450 inducer
	Ritonavir	See above. Ritonavir is also a CYP3A4 substrate and a potent CYP450 inducer

Table 5. (cont.) Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP450 Inducers	Carbamazepine	Carbamazepine is likely to significantly decrease plasma voriconazole concentrations and concomitant use is contraindicated
	Delavirdine	See above. Delavirdine is also a CYP3A4 substrate and inhibitor
	Efavirenz	See above. Efavirenz is also a CYP3A4 inhibitor and substrate
	Mephobarbital	Long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations and concomitant use is contraindicated
	Nevirapine	See above. Nevirapine is also a CYP3A4 substrate and inhibitor
	Phenobarbital	Long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations and concomitant use is contraindicated
	Phenytoin	Phenytoin decreased the steady state Cmax and AUC of voriconazole by 50 and 70%, respectively; voriconazole also increases the Cmax and AUC of phenytoin by 70 and 80%, respectively. Phenytoin is also a CYP2C9 substrate
	Rifabutin	Rifabutin is a potent CYP450 inducer and concomitant use with voriconazole is contraindicated
	Rifampin	Rifampin decreases the steady state Cmax and AUC of voriconazole by 93 and 96%, respectively. Co-administration of rifampin with voriconazole is contraindicated
	Ritonavir	See above. Ritonavir is also a CYP3A4 inhibitor and substrate

Table 5. (cont.) Important drug interactions observed with voriconazole (48)

Mechanism of interaction	Drug	Comment
CYP450 Inducers	Saint John's wort	A 59% decrease in mean voriconazole AUC is observed after multiple doses of St John's Wort, which is also a P-gp inducer. Concomitant use is contraindicated
	Warfarin	Concomitant use with voriconazole with oral coumarin anticoagulants may increase prothrombin time by 2 times. Warfarin is also a CYP2C9 substrate
CYP450 inhibitors	Cimetidine	Cimetidine increases voriconazole Cmax and AUC by 18 and 23%, respectively
CYP2C9 substrates	Methadone	See above. Methadone is also a substrate for CYP3A4 and CYP2C19
	Glipizide	Voriconazole may increase plasma concentrations of sulfonylureas that are substrates for the CYP2C9 and lead to hypoglycaemia
	Glyburide	Voriconazole may increase plasma concentrations of sulfonylureas that are substrates for the CYP2C9 and lead to hypoglycaemia
	Tolbutamide	Voriconazole may increase plasma concentrations of sulfonylureas that are substrates for the CYP2C9 and lead to hypoglycaemia
	Phenytoin	See above. Phenytoin is also a potent CYP450 inducer
	Warfarin	See above. Warfarin is also a CYP3A4 substrate
	Zolpidem	Zolpidem concentrations may be increased with concurrent voriconazole use
CYP2C19 substrates	Methadone	See above. Methadone is also a substrate for CYP3A4 and CYP2C9
	Omeprazole	See above. Omeprazole is also a CYP2C19 inhibitor and a CYP3A4 substrate
CYP2C19 inhibitors	Omeprazole	See above. Omeprazole is also a substrate for CYP2C19 and CYP3A4
	Contraceptives	See above. Oral contraceptives are also CYP3A4 substrates

TDM = therapeutic drug monitoring

2.3.4 Food

The effect of food on the pharmacokinetics of voriconazole was studied in healthy male volunteers. Single and multiple oral administration of voriconazole 200 mg with food lowered the bioavailability by approximately 22% and delayed absorption by a mean of 1.1 hours compared with drug administration in the fasted state (51). Multiple dose administration of voriconazole with high fat meals reduced mean C_{max} and AUC_{τ} values by 34% and 24%, respectively. For this reason oral dose administration was recommended either 1 hour before or 1 hour after meals (46).

2.3.5 Age

a. Geriatrics

In an oral multiple dose study the mean C_{max} and AUC_{τ} in healthy elderly males ($\geq$65 years) were 61% and 86% higher, respectively, than in young males (18-45 years) (46). No significant differences in the mean C_{max} and AUC_{τ} were observed between healthy elderly females ($\geq$65 years) and healthy young females (18-45 years). In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (> 65 years) were approximately 80% to 90% higher than those in the younger patients ($\leq$ 65 years) after either IV or oral administration (46). However, the safety profiles of voriconazole in young and elderly subjects were similar, therefore, no dosage adjustment was necessary for the elderly (46).

b. Pediatrics

For children under the age of 12 years, clinical studies revealed that voriconazole in paediatric doses followed near-linear pharmacokinetics, and

clearance is more rapid, requiring higher doses to achieve AUCs similar to those in adults (22). A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2 to <12 years old who were included in two pharmacokinetic studies of intravenous voriconazole (single dose and multiple doses) (46). Twenty-four of these patients received multiple intravenous maintenance doses of 3 mg/kg and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults (medians of 1.19 μg/mL and 1.16 μg/mL in children and adults, respectively) (46).

c. Adolescents

A pharmacokinetic study was conducted in 26 immunocompromised adolescents aged 12 to less than 17 years following intravenous voriconazole to oral switch regimens: 6 mg/kg IV every 12 h (q 12 h) on day 1 followed by 4 mg/kg IV q 12 h, then switched to 300 mg orally q 12 h (52). Area under the curve over a 12-hour dosing interval (AUC_{0-12}) was calculated using a noncompartmental method and compared to the value for adults receiving the same dosing regimens. On average, the AUC_{0-12} in adolescents after the first loading dose on day 1 and at steady state during IV treatment were 9.14 and 22.4 μg.h/mL, respectively (approximately 34% and 36% lower than values for adults, respectively). At steady state during oral treatment, adolescents also had lower average exposure than adults (16.7 versus 34.0 μg.h/mL). Larger intersubject variability was observed in adolescents than in adults. There was a slight trend for some young adolescents with low body weight to have lower voriconazole exposure. It was likely that these young adolescents may metabolize voriconazole more similarly to children than to adults. Overall, with the same dosing regimens, voriconazole exposures in the majority of adolescents were comparable to those in adults (52). The young adolescents with low body weight during the transitioning period from childhood to

adolescence (e.g., 12 to 14 years old) may need to receive higher doses to match the adult exposures. Safety of voriconazole in adolescents was consistent with the known safety profiles of voriconazole (52).

2.3.6 Hepatic impairment

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the average systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function (53). There was no difference in average peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic insufficiency were compared to controls, there was still a 2.3-fold increase in the average AUC in the group with hepatic insufficiency compared to controls. In an oral multiple dose study, AUC_{τ} was similar in 6 subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard maintenance dose of 200 mg twice daily. The average peak plasma concentrations (C_{max}) were 20% lower in the hepatic impairment group. It was recommended that the standard loading dose regimens could be used but that the maintenance dose should be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) (21, 53).

2.3.7 Renal impairment

In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment (21). Therefore, no adjustment was necessary for oral dosing in patients with mild to severe renal impairment. In a multiple dose study of IV voriconazole (6

mg/kg IV loading dose x 2, then 3 mg/kg IV x 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 subjects with normal renal function (21). However, in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), accumulation of the intravenous vehicle, sulfobutylether-beta-cyclodextrin (SBECD), could occured. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group (54). Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justified the use of intravenous voriconazole (10). A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole was dialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, was hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session did not remove a sufficient amount of voriconazole to warrant dose adjustment (46).

2.3.8 Obese patients

The $AUC_{0-\tau}$ values observed in obese subjects were comparable to those from a historical data set of non-obese subjects (55). Voriconazole dose-normalized $AUC_{0-\tau}$ values had a modestly better correlation with lean body weight (r^2 = 0.42) than total body weight (r^2 = 0.14). An excellent linear relationship (r^2 = 0.96) was identified between C_{min} values and $AUC_{0-\tau}$ value (55). A retrospective study of 92 patients with hematologic malignancies and/or hematopoietic stem cell transplant demonstrated that patients with higher body mass index (BMI) tended to have significantly higher median random voriconazole levels with intravenous administration (6.4 mg/L for BMI $\geq$ 25 kg/m^2 vs 2.8 mg/L for BMI < 25 kg/m^2, p = 0.04). This trend was more notable with the IV than the oral formulations. With the oral formulation, patients with a BMI of $\geq$ 25 kg/m^2 had a median random level of 2.8 mg/L compared with 2.0 mg/L

in patients with a BMI < 25 kg/m^2 (p = 0.18). Patients with a BMI of $\geq$ 25 kg/m^2 also received a higher median daily voriconazole dose (640 mg vs 400 mg, p < 0.001). Standard voriconazole dosing based on actual body weight in obese and overweight patients resulted in higher associated serum concentrations. Dosing based on adjusted body weight may be necessary in this population in order to achieve optimal concentrations while preventing the potential for increased toxicity (56). These findings were in line with the results of Koselke's study which compared voriconazole serum trough levels and toxicities between obese (BMI > 35 kg/m^2) and normal-weight (BMI 18.5–24.9 kg/m^2) patients receiving 4 mg/kg voriconazole every 12 h. They found that the obese group (n = 21) had significantly higher mean voriconazole C_{tr} than the normal-weight group (n = 66) (6.2 and 3.5 mg/L, respectively, p < 0.0001) (57). Patients in the obese group also had higher rates of supratherapeutic voriconazole concentrations (> 5.5 mg/L) than those in the normal-weight group (67% vs 17%, respectively, p < 0.0001). However, the rates of hepatotoxicity and neurotoxicity did not differ between groups. When dosed at 4 mg/kg based on ideal body weight, adjusted body weight and actual body weight in the obese patients, the mean voriconazole C_{tr} were statistically significantly different at 3.95, 3.3 and 6.2 mg/L, respectively (p = 0.0009). Therapeutic voriconazole concentrations (2.0–5.5 mg/L) occurred in 29% of obese patients when dosed on actual body weight, and 45% and 80% of patients when dosed on ideal body weight and adjusted body weight, respectively. These results suggested a strong association between supratherapeutic concentrations and morbidly obese patients when dosed at 4 mg/kg actual body weight. Dosing voriconazole based on an ideal body weight or adjusted body weight may be appropriate for morbidly obese patients (57).

2.4 Voriconazole dosing

Loading doses with the use of both oral and IV formulations have been recommended to expedite steady state (10). For IV administration in patients 12

years and older, 6 mg/kg twice daily for 2 doses, followed by 4 mg/kg IV twice daily until complete the duration of therapy was recommended. The oral dosages in adults were weight based. For those weighing ≥ 40 kg, 400 mg twice daily for 2 doses, followed by 200 mg twice daily for the duration of therapy was suggested, while those weighing < 40 kg should receive 200 mg twice daily for 2 doses followed by 100 mg twice daily (10).

Pediatric patients were known to rapidly metabolize voriconazole, therefore, an IV dose of 7 mg/kg twice daily and oral dosing of 200 mg twice daily without loading was recommended (46).

Dose adjustments were necessary for patients with liver dysfunction which defined as child-pugh class A and B. In these patients, standard loading doses should be given, but with the maintenance dose should be reduced by 50%. There were no dosage recommendation for patients with child-pugh class C and the safety of voriconazole used in severe liver disease remained uncertain (58). Dosage adjustment was not required if oral drug was administered to patients with renal insufficiency. However, IV formulation of voriconazole contained a cyclodextrin vehicle and caused concerns about vehicle accumulation in renal insufficiency or dialysis dependent patients. Intravenous administration of voriconazole should be avoided in patients with a Cl_{Cr} < 50 mL/min unless potential benefit outweighs risks (10).

Similar to the other azoles, voriconazole was teratogenic in animals and was best avoided during pregnancy or while the mother was breastfeeding (59).

3. Voriconazole concentration and clinical outcomes

A multicenter retrospective study (n = 201) found the association between voriconazole trough concentration of < 1.7 mg/L and significantly incidence of treatment failure for invasive fungal infection (IFI) and between trough concentration of > 5 mg/L and neurotoxic adverse events. Increasing patient weight, oral

administration of voriconazole, and coadministration of phenytoin or rifampin were correlated with significantly reduced voriconazole trough concentrations, whereas patient age and coadministration of proton pump inhibitors or corticosteroids were increased voriconazole trough concentration (60). Another retrospective cohort study collected data from 25 patients treated in solid organ and bone marrow transplant units in a tertiary-referral hospital and received voriconazole for treatment of proven or probable IFI observed a large interpatient and intrapatient variability of plasma trough voriconazole concentrations, with no correlation between dose and concentration ($r = 0.065$) (61). Classification and regression tree analysis revealed an association between IFI-related mortality and initial (within 10 days after voriconazole initiation) trough voriconazole concentrations, with patients more likely to die when their initial trough concentration was $\leq$ 0.35 mg/L ($p = 0.004$; OR = 11, 95% CI = 2.9-41.2). Successful outcomes were more likely among patients with a median trough voriconazole concentration > 2.2 mg/L ($p = 0.003$; OR = 2.7, 95% CI = 1.4-5). Patients with severe adverse events had higher median voriconazole concentration than the remaining cohort (2.38 mg/L vs 1.30 mg/L; $p < 0.04$). Therefore, the authors recommended that voriconazole therapeutic drug monitoring was appropriate for all patients as soon as steady statewais achieved (61). For non-responding patients with low trough concentrations, the association with IFI-related mortality indicated the need for dose adjustments to achieve and sustain voriconazole concentration (61). Pascual's group also demonstrated the association between voriconazole trough concentration and responses (17). Lack of response to therapy was more frequent in patients with voriconazole trough level $\leq$ 1 mg/L than in those with voriconazole trough level > 1 mg/L (46% vs 12%; $p = 0.02$). Among patients with voriconazole trough levels > 5.5 mg/L, 5/16 patients (31%) presented with an encephalopathy, whereas, none of the patients with levels $\leq$ 5.5 mg/L presented with neurological toxicity ($p = 0.002$) [16]. In addition, there were some studies reported the association between voriconazole trough concentration and adverse events. Kim's group found that a trough concentration of $\geq$ 5.83 mg/L was a

significant independent risk factor of a severe adverse event (62). The sustained high trough voriconazole concentration of more than 4 mg/L may increase the risk of hepatotoxicity (63). Conversely, some studies reported that voriconazole drug levels were not associated with either clinical outcomes or adverse events (64, 65). Other than above-mentioned studies, there were a number of trials that studied the relationship between voriconazole concentrations and clinical outcome, both efficacy and safety, as shown in Table 6 and 7, respectively.

Table 6 Summary of studies evaluating the relationship between voriconazole trough concentration and clinical efficacy

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration–response relationship	Conclusions
(17)	Single-center observational study (patients receiving TDM were evaluated prospectively; patients not receiving TDM were evaluated retrospectively)	52 adults (of 96 study patients) had VRZ dosages adjusted with TDM (all were white)	Various VRZ doses for treatment of various fungal infections	Yes	No correlation found between VRZ dose and trough concentration (r^2 = 0.07); lack of response in patients with VRZ trough ≤ 1 μg/ml vs > 1 μg/ml: 46% vs 12% (p = 0.02); logistic regression showed that VRZ trough concentration is a significant predictor of response to therapy: 70% probability of response at trough of 1 μg/ml
(15)	Open-label noncomparative multicenter study	137 patients aged ≥ 14 y with invasive aspergillosis	Two loading doses of VRZ 6 mg/kg IV, then 3 mg/kg IV q12 h, then 200 mg orally twice/day for 4–24 wks	Yes	60% of patients with VRZ troughs < 0.25 μg/ml failed therapy; 40% had either stable response or deteriorated and then improved after dose escalation
(60)	Multicenter retrospective study	201 adults with at least one administered VRZ dose and one VRZ concentration	85% received treatment doses vs 15% prophylactic doses; 97 patients received oral VRZ, 76 received IV and oral VRZ, and 28 received IV VRZ	Yes	Median VRZ concentration was significantly lower in patients who failed therapy (0.9 μg/ml) vs patients who had treatment success (2.1 μg/ml, p<0.05); VRZ concentration was a significant predictor of treatment success; VRZ concentration ≥ 1.7 μg/mL minimized the incidence of treatment failure (p < 0.05)

Table 6. (cont.) Summary of studies evaluating the relationship between voriconazole trough concentration and clinical efficacy

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration–response relationship	Conclusions
(66)	Retrospective study	28 patients who received VRZ and were monitored for therapeutic concentrations due to disease progression or adverse events	All patients received a VRZ loading dose and 200 mg orally twice/day for at least 2 wks	Yes	100% of patients who had treatment failures (n=17) had VRZ concentrations ≤ 2.51 μg/ml; VRZ concentration < 2 μg/ml prompted dose increases in 11 patients, and 8 of the 11 patients survived; disease progression was significantly associated with VRZ concentration ($p < 0.025$); 100% (10/10) of patients with random concentrations >2.05 μg/ mL had positive clinical responses; 8/18 patients died who had random concentrations < 2.05 μg/ mL
(67)	Prospective clinical study	29 Japanese patients	6 mg/kg twice/day for 1 day, then 3.6 ± 0.8 mg/kg twice/ day	Yes	VRZ response was observed in 21/29 patients (72%) who had troughs ≥ 1.2 μg/ mL; troughs < 1.2 μg/mL were associated with treatment failure

Table 6. (cont.) Summary of studies evaluating the relationship between voriconazole trough concentration and clinical efficacy

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration–response relationship	Conclusions
(68)	Prospective clinical study	34 adult Japanese patients with hematologic disorders	Investigators conducted TDM and analyzed VRZ plasma concentrations; oral VRZ was initially used according to the manufacturer's recommendation; if oral was not tolerated, patients were switched to IV VRZ	Inconclusive findings	100% of patients who had troughs >2 μg/ml responded vs 33.3% of patients with troughs <2 μg/ml failed therapy; recommended trough range: 2–6 μg/ml
(69)	Observational analysis of data from 9 phase II and phase III clinical trials completed before 2000	825 patients receiving VRZ for primary or salvage therapy	Various VRZ doses; patients had recorded clinical responses and VRZ plasma concentrations from a total of 3,052 plasma samples	Yes	Logistic modeling revealed a significant nonlinear relationship between mean VRZ plasma concentration and clinical response ($p < 0.003$); probability of maximum clinical response was best with trough: MIC ratio of 2–5; better efficacy observed with primary therapy, yeast infections, candidiasis, and lower baseline bilirubin and alkaline phosphatase levels

Table 6. (cont.) Summary of studies evaluating the relationship between voriconazole trough concentration and clinical efficacy

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration–response relationship	Conclusions
(70)	Retrospective study	46 pediatric patients from a pediatric referral hospital	Various VRZ doses; patients had recorded clinical responses and VRZ plasma concentrations from a total of 227 concentrations	Yes	Each VRZ trough concentration <1 μg/ml was associated with a 2.6 fold increase in the odds of death

Adapted from Obeng AO et. al. (43)

Although voriconazole showed excellent antifungal activity, there were many concerns about its use. Voriconazole exhibited non-linear pharmacokinetic behavior and the plasma concentrations showed large inter- and intraindividual variability with many factors influencing its pharmacokinetics. Although receiving the same recommended dosage regimen, the plasma concentrations were ranging from 0.2 to 12 μg/mL and there were a number of prior studies reported that the plasma voriconazole concentration was associated with both efficacy and adverse effects (17, 60, 67). The voriconazole concentration that caused therapeutic effect was closed to the concentration that caused adverse effects, i.e., narrow therapeutic index. For these reasons, therapeutic drug monitoring may ameliorate the efficacy and safety in invasive fungal diseases therapy by voriconazole. Because of the large pharmacokinetic variability and the lacking of pharmacokinetic data in Thai patients, the pharmacokinetic study of voriconazole in this patient group was necessary.

Table 7 Summary of studies evaluating the relationship between voriconazole concentration and adverse events

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration– response relationship	Conclusions
(36)	Retrospective analysis	37 Japanese children	Patients received IV VRZ at a median dose of 7.7 mg/kg/day (range 3.5–18.8 mg/kg/day); patients were genotyped for CYP2C19 *2, *3, and *17 alleles	No	Severe hepatotoxicity was not associated with high voriconazole exposure
(17)	Single-center observational study (patients receiving TDM were evaluated prospectively; patients not receiving TDM were evaluated retrospectively)	52 adults (of 96 study patients) had VRZ dosages adjusted with TDM (all were white)	Various VRZ doses for treatment of various fungal infections	Yes	Neurologic AEs occurred more frequently in patients with troughs >5.5 μg/ml vs patients with troughs ≤ 5.5 μg/ ml (p=0.002) after 1 wk of therapy; logistic regression confirmed significant association between VRZ trough concentration and neurotoxicity: odds ratio after a 2-fold increase of VRZ concentration = 284 (95% confidence interval 0.96–84,407, p=0.05); 15% probability of neurotoxicity at trough of 5.5 μg/ml vs 90% at 8 μg/ml; trend showed increased hepatotoxicity in patients with troughs > 5.5 μg/ml vs patients with troughs ≤ 5.5 μg/ ml: 19% vs 8% (p=NS)

Table 7. (cont.) Summary of studies evaluating the relationship between voriconazole concentration and adverse events

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration– response relationship	Conclusions
(60)	Multicenter retrospective study	201 adults with at least one administered VRZ dose and one VRZ concentration	85% received treatment doses vs 15% prophylactic doses; 97 patients (48%) received oral VRZ, 76 received IV and oral VRZ, and 28 received IV VRZ	Yes	21 patients (10.5%) had neurotoxic AEs (visual or auditory hallucinations); median trough was higher in patients with AEs vs those without AEs: 6.5 vs 1.6 μg/ml ($p<0.01$); trough concentration <5 μg/ml was found to minimize neurologic AEs ($p<0.001$); all AEs resolved after VRZ discontinuation or dosage reduction
(53)	Retrospective clinical study; analysis of safety and pharmacokinetic data from 10 phase II and phase III therapeutic trials	1053 patients (81.8% white, 9.8% AfricanAmerican, 8.5% Asian)	VRZ empiric and treatment doses; 1053 patients had a total of 2925 plasma voriconazole concentrations	Yes	Relationship between plasma VRZ concentration and visual AEs ($p=0.011$); weaker but statistically significant association with VRZ plasma concentration and AST, ALP, or bilirubin level, but not ALT level, abnormalities; 1-μg/ml elevation of VRZ concentration increased odds of LFT abnormalities from 1.07 –1.17; individual VRZ plasma concentration cannot predict subsequent LFT abnormalities according to receiver operating characteristic curve analysis

Table 7. (cont.) Summary of studies evaluating the relationship between voriconazole concentration and adverse events

Ref	Study design	Patient population	Intervention	Demonstrated VRZ concentration– response relationship	Conclusions
(67)	Prospective clinical study	29 Japanese patients	6 mg/kg twice/day for 1 day, then 3.6 ± 0.8 mg/kg twice/day	Yes	Hepatotoxicity (CTCAE v.3)[a] associated with troughs > 4 μg/ml in 9 of 12 patients ($p < 0.01$); trough was a predictor of hepatotoxicity
(15)	Open-label noncomparative multicenter study	137 patients ≥14 yrs of age with invasive aspergillosis	Two loading doses of VRZ 6 mg/kg IV, then 3 mg/kg IV 12 h, then 200 mg orally twice/day for 4–24 wks	Inconclusive findings	6 of 22 patients (27.3%) with VRZ troughs > 6 μg/ml developed abnormal liver function (>3 or 5 times the upper limit of normal) or liver failure (not defined in this study)

Adapted from Obeng AO et. al. (43)

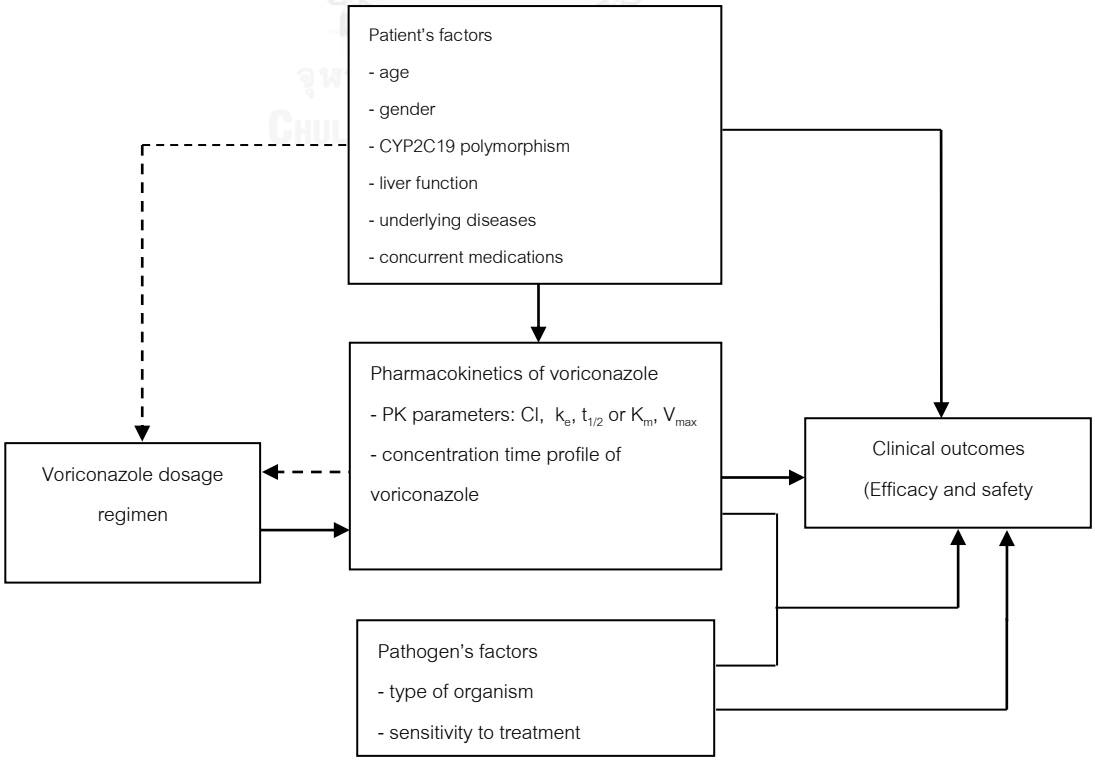
CHAPTER III

MATERIALS AND METHODS

1. Scope of Research (study design, population and sample, setting, duration)

This retrospective study was performed in Thai adult patients who were diagnosed invasive aspergillosis and received voriconazole as an anti-fungal treatment at Ramathibodi Hospital during January 2013 to March 2016. It aimed to identify correlation between patient's factors and voriconazole pharmacokinetic parameters, and relationship between voriconazole concentration and clinical outcome in Thai adult patients. The protocol was approved by the institution review board, Faculty of Medicine Ramathibodi Hospital, Mahidol University (for more information see Appendix A).

1.1 Conceptual framework



1.2 Population and sample

Population: Thai adult patients who were diagnosed invasive aspergillosis and received voriconazole as an anti-fungal treatment at Ramathibodi Hospital during January 2013 to March 2016

Sample: Subjects would eligible for this study if they met these following inclusion and exclusion criteria

This study was separated into 2 parts to serve 2 study's objectives which are: (i) part A: nonlinear pharmacokinetic study of voriconazole in Thai adult patients, and (ii) part B: clinical outcome assessment and factors influencing clinical outcome. Part A aimed to determine pharmacokinetic parameters (K_m, V_{max}) of voriconazole in Thai adult patients and identify correlation between the factors (e.g., *CYP2C19* polymorphism, patient's demographic data, laboratory data, etc.) and voriconazole pharmacokinetic (PK) parameters and develop the model to predict pharmacokinetic parameters. Part B aimed to identify association between pharmacokinetic parameters (C_{tr}), pharmacodynamic (PD) parameters (MIC (if available)), or PK/PD parameters (C_{tr}/MIC) and clinical outcome.

Inclusion criteria

For part A: nonlinear pharmacokinetic study of voriconazole in Thai adult patients

1. Adult patients with age over than 18 years old.
2. Patients with diagnosis of possible, probable, or proven invasive aspergillosis.
3. Patients who received voriconazole as antifungal treatment during January 2013 to March 2016.

4. Patients who were received two different doses of voriconazole and had at least one trough concentration for each dose.

For part B: clinical outcome assessment and factors influencing clinical outcome

1. Adult patients with age over than 18 years old.
2. Patients with diagnosis of possible, probable, or proven invasive aspergillosis.
3. Patients who received voriconazole as antifungal treatment during January 2013 to March 2016.

Exclusion criteria

For part A: nonlinear pharmacokinetic study of voriconazole in Thai adult patients

1. Patients with severe hepatic impairment defined as CTCAE (Common Terminology Criteria for Adverse Events) grade ≥ 4. (see Appendix B)
2. Pregnant women and women with child bearing potential.

For part B: clinical outcome assessment and factors influencing clinical outcome

1. Patients with severe hepatic impairment defined as CTCAE (Common Terminology Criteria for Adverse Events) grade ≥ 4. (see Appendix B)
2. Pregnant women and women with child bearing potential.
3. Patients whose data was not sufficient for clinical outcome assessment. (for part B: clinical outcome assessment group)

1.3 Sample size calculation

Assumed that the predictor with the coefficient of determination (r^2) of 30% or 0.3 was considered as a significant predictor. The sample size for pharmacokinetic study could be calculated by the test of significance of one correlation as following formula.

$$n = \left\{\frac{Z_{\alpha/2} + Z_{\beta}}{F(Z_0) + F(Z_1)}\right\}^2 + 3$$

$$F(Z) = 0.5ln\left(\frac{1+\rho}{1-\rho}\right)$$

where

H_0: ρ_0 = 0 (no correlation)

H_1: ρ_1 = 0.5477 (r^2 = 0.3 so r = $\sqrt{0.3}$ = 0.5477)

$Z_{\alpha/2}$ = $Z_{0.025}$ = 1.96

Power = 80%

β = 0.2

Z_{β} = $Z_{0.2}$ = 0.842

under H_0: ρ_0 = 0

$$F(Z_0) = 0.5ln\left(\frac{1+0}{1-0}\right) = 0$$

under H1: ρ_1 = 0.5477

$$F(Z_1) = 0.5ln\left(\frac{1+0.5477}{1-0.5477}\right) = 0.6151$$

So

$$n = \left\{\frac{Z_{\alpha/2} + Z_{\beta}}{F(Z_0) + F(Z_1)}\right\}^2 + 3$$

$$n = \left\{\frac{1.96 + 0.842}{0 + 0.6151}\right\}^2 + 3$$

$$n = 23.75$$

$$\sim 24$$

1.4 Operational definition

1.4.1 IFD diagnosis

IFD was classified into three classes which are proven, probable, and possible IFD.

- **Proven IFD** was defined as microscopic analysis of sterile material revealed histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage or culture of sterile material found recovery of a mold or “black yeast” by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine.
- **Probable IFD** was defined as positive signs of fungal infection on imaging (CT scan or MRI) such as dense, well-circumscribed lesions(s) with or without a halo sign or air-crescent sign or cavity for lunf infection together with positive laboratory test of fungal infection (i.e., galactomannan for aspergillus infection).
- **Possible IFD** was defined as positive either signs of fungal infection on imaging or positive laboratory test of fungal infection.

1.4.2 Voriconazole trough concentration

In this study, blood samples for voriconazole measurement were drawn approximately half hour before next dose. The time after last administered dose were ranging from 9 to 14 hours depending on meal time. To evaluate the relationship between voriconazole concentration and clinical outcomes, in term of efficacy and safety, the most current steady state voriconazole trough levels before treatment outcome or toxicity assessment were used.

1.4.3 Treatment outcome

Treatment response had been assessed as following:

a. Successful was classified into two types of response which were complete response and partial response.

- Complete response: Survival within the pre-specified period of observation, and

resolution of all attributable symptoms and signs of infection and radiological abnormalities, and mycological evidence of eradication of infection.

- Partial response: Survival within the pre-specified period of observation, and improvement in attributable symptoms and signs of infection and radiological abnormalities, and evidence of sterilization of cultures or reduction of fungal burden assessed by a quantitative and validated laboratory marker.

b. Failure was classified into three groups; stable response, progression of fungal disease, and death.

- Stable response: Survival within the pre-specified period of observation and minor or no improvement in fungal disease, but no evidence of progression, based on a composite of clinical, radiologic, and mycologic criteria; or

- Progression of Fungal Disease: Evidence of progressive fungal disease based on a composite of clinical, radiologic, and mycologic criteria; or

- Death: Death during the pre-specified period of evaluation regardless of attribution.

c. Non-evaluable or indeterminate was inability to assess global response. Potential reasons included inadequate diagnostic evaluation, conflicting clinical, radiographic, or mycological data, or presence of other factors such as an unrelated infection or relapse of malignancy that confound assessment of response to antifungal therapy.

1.4.4 Drug-induced liver injury (DILI) or hepatotoxicity (71)

Patients would be counted for developed DILI or hepatotoxicity if they had abnormal liver function tests (LFTs) at least one of following criteria.

- ALT level > 3 times ULN and symptomatic (nausea, vomiting, abdominal pain, jaundice); or
- ALT level > 5 times ULN and asymptomatic; or
- Total serum bilirubin concentration > 2 times ULN.

2. Data collection

The eligible patients were included into the study and their hospital medical records were be reviewed for these following information

- Patient demographic data e.g. age, gender weight, ward of admission
- Clinical data such as underlying diseases, clinical signs and symptoms, history of allergy
- Laboratory data such as baseline liver function tests (e.g., AST, ALT, ALP, GGT, TB, DB), renal function tests (S_{Cr}, BUN), WBC count
- Radiologic data (CT scan or MRI)
- Pharmacogenetic data: CYP2C19 polymorphism
- Voriconazole dosage regimen and concentraton
- Microbiological data including infection focus, organism, culture and sensitivity tests
- Medication that potentially interacted with voriconazole such as proton pump inhibitors, steroids, co-trimoxazole, other antifungals

3. Blood sampling and specimen

3.1 Measurement of voriconazole levels (26)

Blood sample was collected at steady state (at least 5 days after voriconazole initiation) before next dose (C_{tr}). Time after last administration dose to blood sampling (TAD) may vary depended on meal time. In this study, voriconazole concentrations with TAD ranging from 9-14 hours were considered to be trough concentration (C_{tr}). Voriconazole concentration were measured by validated method using LC/MS/MS performed by pharmacogenomics or toxicology laboratory, Faculty of Medicine, Ramathibodi Hospital, Thailand. Blood samples from each patient were collected into EDTA tubes. Plasma was collected by centrifugation at 3000 rpm for 15 min. Standard solutions were prepared at eight concentrations; 10,000, 5000, 2500, 1200, 800, 400, 100 and 50 ng/ml, respectively. Fluconazole was used as an internal standard (IS). Samples (100 ml) were precipitated protein by 100% Acetonitrite (200 ml) and vortex-mixed (60 s) and centrifuged (MIKRO 200) at 15,000 rpm for 5 min, then vacuum dried at 50 °C for 1 h and 50 min. 0.1% formic acid in 10 mM ammonium acetate-acetronitrile (50:50) (100 ml) was added before further centrifugation at a speed of 15,000 rpm for 5 min. The supernatant was analyzed with LC/MS/MS Model API 3200. The Linear Regression Equation for measurement of voriconazole in the bloodstream was calculated from an average of three samples from each patient: $y = 0.01334X + 3.1$, $r = 0.9994$.

3.2 DNA extraction and diagnosis of polymorphism in CYP2C19 (26)

DNA extraction

Blood samples were collected from all individuals into ethylenediaminetetraacetic acid (EDTA) tubes. Genomic DNA was extracted from whole blood using the MagNa Pure automated extraction system according

to the manufacturer's instructions. The quantity and purity of the extracted DNA was assessed with a Nanodrop ND-1000. DNA concentration was subsequently adjusted to a concentration of 5 ng/ml. The samples were stored at -80 °C.

Diagnosis of polymorphism in CYP2C19

The genetic material (DNA) extracted from each subject's blood sample was analyzed by LightMix® to detect human CYP2C19*2 and CYP2C19*3 sequences. LightMix® uses principles of Real-time PCR with a growing number of CYP2C19 genes and the divergent alleles (CYP2C19*2 and CYP2C19*3). Probe specificity of CYP2C19*2 was checked by SimpleProbe®. CYP2C19*3 was checked with LightCycler® Red 640, and then analyzed and interpreted for patterns indicating abnormal genotype. For the divergence of gene CYP2C19*17 was analyzed using a series of tests TaqMan® Drug Metabolism Genotyping Assays by increasing the gene CYP2C19 with primers that are specific and the divergence of alleles with specific TaqMan® MGB probes (FAMTM and VIC® dye-labeled) and TaqMan® MGB probes were labeled with reporter dye and quencher dye, which can emit light at different wavelengths. Genetic variations of the gene CYP2C19 can be analyzed by the ratio of the fluorescence signal of the wild-type and mutant probes. The presence of the wild type allele CYP2C19*1 was inferred from the absence of the *2, *3 and *17 alleles.

4. Data analysis

4.1 Part A: Nonlinear pharmacokinetic study of voriconazole in Thai adult patients

4.1.1 Pharmacokinetic parameters estimation

To estimate voriconazole pharmacokinetic parameters (K_m and V_{max}), we used Michaelis-Menten equation (eq. 1) which two dosing rates (R) and voriconazole Ctr

from each dose were required. K_m and V_{max} could be calculated by equation 2 and 3, respectively.

$$R = \frac{V_{max} \cdot C}{K_m + C} \quad (1)$$

$$K_m = \frac{R_1 - R_2}{\frac{R_1}{C_1} - \frac{R_2}{C_2}} \quad (2)$$

$$V_{max} = K_m \left(\frac{R}{C}\right) + R \quad (3)$$

Where R = dosing rate (mg/kg/h)

V_{max} = maximum metabolism rate (mg/kg/h)

K_m = VRZ concentration at half V_{max} (mg/L)

C = VRZ trough concentration (mg/L)

Then the calculated K_m and V_{max} calculation would be futher used to estimate the recommend dosing rate (R) for our patient group using equation 4. After round up the dose, voriconazole trough concentration could be estimated by equation 5.

$$R = \frac{V_{max} \cdot C}{K_m + C} \quad (4)$$

$$C = \frac{K_m \cdot R}{V_{max} - R} \quad (5)$$

Furthermore, the times to reach 90% of steady state ($t_{90\%}$) were then be calculated to indicate the appropriate blood sampling time for voriconazole level measurement using equation 6.

$$t_{90\%} = \frac{K_m \cdot V \ (2.3V_{max} - 0.9R)}{(V_{max} - R)^2} \quad (6)$$

$t_{90\%}$ = time to reach 90% of steady state (3.3 $t_{1/2}$)

V = volume of distribution of VRZ = 4.2 L/kg

4.1.2 Statistical analysis

Descriptive statistics such as percentage, mean, standard deviation, median, interquartile range were used to describe demographic data and other variables in the study. To determination of patient's factors that influenced pharmacokinetic parameters, Correlation test (Spearman rank correlation for categorical data and by Pearson's correlation for continuous data) was used. ANOVA or Kruskal-wallis test was used to compare mean or median of K_m and V_{max} across group. Stepwise multiple linear regression was used to built the model for K_m and V_{max} prediction. Statistical significance was defined by 2-sided p value < 0.05 for all tests. The analysis was performed with SPSS (Statistical Package for the Social Sciences, version 22, SPSS Inc., Chicago, IL).

4.2 Part B: Clinical outcome assessment and factors influencing clinical outcome

4.2.1 Statistical analysis

Categorical variables were reported as frequencies and percentages. Optimal therapeutic range was selected considering the range with high success rate together with low adverse events rate.

5. Ethical Consideration (For more information see Appendix C)

This study was planned and conducted in agreement with the principles as stated in the Declaration of Helsinki after approval by an independent Ethics Committee (Faculty of Medicine Ramathibodi Hospital, Mahidol University). The process for obtaining participant informed consent was in accordance with the Recruitment & Employment Confederation (REC) guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator had informed the participant of any relevant information that became available during the course of the study, and discussed with them, whether they

wished to continue with the study. The decision regarding participation in the study was entirely voluntary. The investigator emphasized to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant was otherwise entitled. The investigator and the participant both sign and date the Consent Form when they could.

CHAPTER IV

RESULTS AND DISCUSSION

RESULTS

Part A: Nonlinear pharmacokinetic study of voriconazole in Thai adult patients

1. Subjects and clinical characteristics

The blood samples of 53 adult patients with IA who were treated with VRZ were analyzed for their plasma VRZ C_{tr} in this study. The demographic and clinical characteristics of the patient population were summarized in Table 8. Median age and body weight of the patients was 52.98 ± 15.64 y and 57.97 ± 9.99 kg, respectively. Just over half (n = 29, 54.7%) of the patients were male. Underlying diagnoses were hematological malignancies (n = 42), immunosuppressive therapy (n = 3), solid tumor (n = 3) and HIV infection (n = 1). The major *Aspergillus* infection site was the lung (n = 42, 79.25%) followed by the sinus. Most patients were diagnosed with probable IA (n = 31), followed by proven IA (n = 12) and possible IA (n = 10), respectively. Considering the baseline laboratory tests, patients in this study had normal renal functions, mild liver disorders and mild anemia.

The number and frequencies of variant alleles of CYP2C19 in this study population were shown in Tables 8. Of those patients, the *1/*1 genotype was the majority (n = 26, 49.1%) followed by *1/*2 (n = 19, 35.8%). With respect to the classification of patients based on the ability to metabolize CYP2C19 substrates, they were 49.1% EM, 41.5% IM and 9.4% PM.

Table 8 Demographic and clinical characteristics of the studied patient population (N = 53)

Characteristics	Number (percentage)
Gender, number (%)	Male: 29 (54.7)
	Female: 24 (45.3)
Age, median ± IQR (range)	52.98 ± 15.64 (18.09–82.48)
Body weight, median ± IQR (range)	57.97 ± 9.99 (38.80–84.00)
Underlying diagnosis	
Hematological malignancies	42 (79.2)
Immunosuppressive therapy	3 (5.7)
Solid tumor	3 (5.7)
HIV/AIDS	1 (1.9)
Other[a]	2 (3.8)
None	2 (3.8)
Aspergillosis infection site	
Lung	42 (79.2)
Sinus	11 (20.8)
IA diagnosis	
Proven	12 (22.6)
Probable	31 (58.5)
Possible	10 (18.9)
Baseline laboratory tests (normal range)[b]	**median ± IQR (N)**
SCr (0.4–1.2 mg/dL)	1.12 ± 0.66 (52)
ClCr (mL/min)	71.95 ± 36.57 (52)
AST (15–37 U/L)	35.90 ± 22.16 (52)
ALT (30–65 U/L)	56.58 ± 547.49 (52)
ALP (50–136 U/L)	187.90 ± 162.92 (52)
GGT (male: 15–85 U/L,	Male:207.03 ± 136.98 (28)
female 5–55 U/L)	Female: 262.2 ± 291.2 (24)
TB (0.2–1.2 mg/dL)	1.11 ± 0.61 (52)
DB (0.0–0.3 mg/dL)	0.63 ± 0.45 (51)
Albumin (35–50 g/L)	25.69 ± 6.25 (51)

Table 8. (cont.) Demographic and clinical characteristics of the study patient population (N = 53)

Characteristics	Data
Baseline laboratory tests (normal range)[a]	**median ± IQR (N)**
WBC (4,000–10,700 cells/cm^3)	5,993.32 ± 7,249.85 (53)
% N (40–74%)	57.80 ± 35.16 (47)
ANC (1,500–8,000 cells/mm^3)	4,982.72 ± 6,821.12 (47)
Hb (male: 14.0–17.5 g/dL,	Male: 9.48 ± 1.42 (29)
female: 12.0–16.0 g/dL)	Female: 9.58 ± 1.42 (24)
Hct (male: 40–54%	Male: 27.72 ± 5.89 (29)
female: 36–48%)	Female: 28.21 ± 4.21 (24)
Plt (140–450 x10^3/mm^3)	133.64 ± 130.59 (53)
CYP2C19 phenotype and genotype	**Number (percentage)**
- Extensive metabolizer; EM (N = 26)	
*1/*1	26 (49.1)
- Intermediate metabolizer; IM (N = 22)	
*1/*2	19 (35.8)
*1/*3	3 (5.7)
- Poor metabolizer; PM (N = 5)	
*2/*2	2 (3.8)
*3/*3	1 (1.9)
*2/*3	2 (3.8)

[a]One hypertension, one diabetes mellitus.

[b]Reference data from clinical pathology laboratory, Ramathibodi hospital, Bangkok, Thailand.

Abbreviation: Alb; albumin, ALP; alkaline phosphatase, ALT; alanine aminotransferase, ANC; absolute neutrophil count, AST; aspartate aminotransferase; Cl_{Cr}; creatinine clearance, DB; direct bilirubin, EM; extensive metabolizer, GGT; γ-glutamyl transpeptidase, Hb; haemoglobin, Hct; haematocrit, IM; intermediate metabolizer, Plt; platelet, PM: poor metabolizer, S_{Cr}; serum creatinine, TB; total bilirubin.

Table 9 Subgroup analysis of demographic and clinical characteristics of the studied patient population across CYP2C19 Phenotype (N = 53)

Characteristic	Median ± IQR		
	EM (n = 26)	Non-EM (n = 27)	p-value
Age	48.37 ± 21.86	57.21 ± 21.55	0.126
Body weight	56.05 ± 9.33	58.00 ± 15.50	0.600
Baseline laboratory tests (normal range) [a]			
SCr (0.4–1.2 mg/dL)	1.12 ± 0.57	0.18 ± 0.58	0.135
ClCr (mL/min)	63.18 ± 31.43	76.59 ± 47.54	0.318
AST (15–37 U/L)	34.00 ± 42.50	25.00 ± 67.00	0.070
ALT (30–65 U/L)	48.00 ± 63.00	40.50 ± 31.75	0.191
ALP (50–136 U/L)	178.00 ± 194.50	121.00 ± 64.00	0.027*
GGT (male: 15–85 U/L, female 5–55 U/L)	253.00 ± 272.25	115.00 ± 134.25	0.079
TB (0.2–1.2 mg/dL)	1.20 ± 0.95	0.85 ± 0.53	0.029*
DB (0.0–0.3 mg/dL)	0.70 ± 0.80	0.40 ± 0.33	0.001**
Albumin (35–50 g/L)	21.85 ± 4.68	27.70 ± 10.05	0.012*
WBC (4,000–10,700 cells/cm^3)	2,525.00 ± 8,732.50	5,020.00 ± 6,570.00	0.439
% N (40–74%)			
ANC (1,500–8,000 cells/mm^3)	3,230.92 ± 6,639.89	3,283.9 ± 6,567.00	0.813
Hb (male: 14.0–17.5 g/dL female: 12.0–16.0 g/dL)	9.35 ± 1.90	9.60 ± 1.90	0.880
Hct (male: 40–54%, female: 36–48%)	28.15 ± 6.13	29.00 ± 6.40	0.936
Plt (140–450 x10^3/mm^3)	104.00 ± 162.50	107.00 ± 141.00	0.838

[a]Reference data from clinical pathology laboratory, Ramathibodi hospital, Bangkok, Thailand.

Abbreviation: Alb; albumin, ALP; alkaline phosphatase, ALT; alanine aminotransferase, ANC; absolute neutrophil count, AST; aspartate aminotransferase; Cl_{Cr}; creatinine clearance, DB; direct bilirubin, EM; extensive metabolizer, GGT; γ-glutamyl transpeptidase, Hb; haemoglobin, Hct; haematocrit, IM; intermediate metabolizer, Plt; platelet, PM: poor metabolizer, S_{Cr}; serum creatinine, TB; total bilirubin.

2. Pharmacokinetic analysis

The patient's factors found to influence the K_m of VRZ were the CYP2C19 phenotype, age, TB, and ALP, while none of patient's factors could predict the V_{max}. The median K_m of VRZ was 2.92-fold lower in the EM than in the non-EM (p-value = 0.008), while the V_{max} was only 1.14-fold lower in the EM than the non-EM, which was not significant (Table 10). The median plasma VRZ C_{tr} after initiation of the same maintenance dose of 8 mg/kg/d, divided into two doses, was 1.1-fold lower in the EM than in the non-EM, but this was not significant (Table 10). Based on the calculated pharmacokinetic parameters (median K_m of 0.262 and 0.666 mg/L for the EM and non-EM groups, respectively, and a median V_{max} of 0.467 mg/kg/h for patients), the optimal VRZ dose was estimated using Eq. (1) to keep the C_{tr} within the therapeutic range of 1.0–5.0 mg/L. The recommended doses then ranged from 8.9–10.7 and 6.7–9.9 mg/kg/d, divided into two equal doses and given every 12 h, for the EM and non-EM groups, respectively, to keep the C_{tr} within the 1.0–5.0 mg/L range, respectively (Table 11).

Table 10 Pharmacokinetic parameters of VRZ classified by CYP2C19 phenotype

CYP2C19 phenotype	Median ± IQR					
	K_m (mg/L)	p-value	V_{max} (mg/kg/h)	p-value	Initial C_{tr} (mg/L)	p-value
EM (n = 26)	0.262 ± 0.29	0.008**	0.425 ± 0.14	0.262	1.870 ± 3.20	0.845
Non-EM (n = 27)	0.666 ± 1.78		0.483 ± 0.25		2.060 ± 4.69	
Total (n = 53)	0.391		0.467			

**statistically significant at $p < 0.01$

To be more applicable in clinical practice, we recommended a VRZ daily dose of 10.3 and 9.2 mg/kg/d for the EM and non-EM, respectively, to keep the plasma VRZ C_{tr} at approximately 3 mg/L. The $t_{90\%}$ for each phenotypic group at each dose was consequently determined, where at the recommended dose (10.3 and 9.2 mg/kg/d

for the EM and non-EM groups, respectively) the $t_{90\%}$ was 20.5 and 16.5 d for the EM and non-EM groups, respectively (Table 12). Therefore, the appropriate blood sampling time for the VRZ C_{tr} measurement was around 21 and 17 d after VRZ initiation for the EM and non-EM patients, respectively, when our recommended dose was used. If patients received a higher dose, the $t_{90\%}$ would be longer.

Table 11 Recommended VRZ dose for IA treatment according to CYP2C19 phenotype

Target C_{tr} (mg/L)	Dose (mg/kg/d)	
	EM	Non-EM
1	8.9	6.7
1.5	9.5	7.8
2	9.9	8.4
2.5	10.2	8.9
3	10.3	9.2
3.5	10.4	9.4
4	10.5	9.6
4.5	10.6	9.8
5	10.7	9.9
Recommended dose (mg/kg/d)	10.3–10.5	9.2-9.6

Additionally, we conducted a correlation test to determine association between patient's factors and pharmacokinetic parameters. The correlation coefficients between patient's factors and K_m and V_{max} were shown in Table 13 and 14, respectively. Then, multiple linear regression were performed to determine the model to predict the K_m and V_{max} for an individual patient that can be used when CYP2C19 polymorphism was not available. The significant predictors for K_m were age, baseline TB and ALP as shown in model 1 (Table 15, adjusted R^2 = 0.262) but none of patient's factors could predict V_{max}. Because V_{max} value did not much differ between each CYP2C19 phenotype, the median value of V_{max} (0.47 mg/kg/h) could be used for each patient. After K_m was estimated by model 1 and V_{max} was fixed to

0.47 mg/kg/h, and required VRZ C_{tr} was selected, dosing rate (R) for each patient then could be calculated using equation 4.

$$\text{Model 1: } K_m = -1.907 + 0.042\text{Age} + 1.195\text{TB} - 0.003\text{ALP}$$

Table 12 Time to reach 90% of steady state ($t_{90\%}$) across the phenotypic groups

Dosing rate	EM		non-EM	
(mg/kg/d)	$C_{tr,SS}$ (mg/L)	$t_{90\%}$ (d)	$C_{tr,SS}$ (mg/L)	$t_{90\%}$ (d)
7	0.44	1.24	1.11	3.70
7.25	0.48	1.39	1.22	4.17
7.5	0.53	1.57	1.34	4.73
7.75	0.59	1.78	1.49	5.42
8	0.65	2.05	1.65	6.28
8.25	0.73	2.38	1.85	7.36
8.5	0.82	2.81	2.08	8.74*
8.75	0.93	3.37	2.36	10.56
9	1.06	4.13	2.70	13.03
9.25	1.32	5.19	3.13	16.50
9.5	1.45	6.73	3.68	21.58
9.75	1.74	9.12	4.43	29.45
10.00	2.15	13.09*	5.47	42.63
10.25	2.78	20.49	7.06	67.26
10.50	3.84	36.82	9.75	121.86
10.75	6.03	85.70	15.32	285.97

* $t_{90\%}$ if the recommended dose (10 and 8.5 mg/kg/d for EM and non-EM, respectively) was administered.

Table 13 Spearman's rho correlations between K_m and patient's factor

Variables	Correlation coefficient	p-value
Gender	0.020	0.888
Age	0.418	0.002
Weight	0.105	0.452
Hematologic malignancies	-0.070	0.619
S_{Cr}	-0.096	0.498
Cl_{Cr}	0.005	0.971
AST	-0.233	0.097
ALT	-0.340	0.014
ALP	-0.366	0.008
GGT	-0.299	0.031
TB	-0.172	0.223
DB	-0.317	0.023
ALB	0.088	0.539
Non-EM	0.370	0.006

Abbreviation: ALB; albumin, ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, Cl_{Cr}; creatinine clearance, DB; direct bilirubin, GGT; γ-glutamyl transpeptidase; Non-EM; non-extensive metabolizer (CYP2C19), S_{Cr}; serum creatinine, TB; total bilirubin.

Table 14 Spearman's rho correlations between V_{max} and patient's factor

Variables	Correlation coefficient	p-value
Gender	-0.107	0.448
Age	0.086	0.540
Weight	-0.239	0.085
Hematologic malignancies	-0.082	0.559
S_{Cr}	-0.066	0.640
Cl_{Cr}	0.018	0.899
AST	-0.256	0.067
ALT	-0.177	0.209
ALP	-0.378	0.006
GGT	-0.206	0.143
TB	-0.011	0.940
DB	0.018	0.900
ALB	-0.172	0.228
Non-EM	0.155	0.266

Abbreviation: ALB; albumin, ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, Cl_{Cr}; creatinine clearance, DB; direct bilirubin, GGT; γ-glutamyl transpeptidase; Non-EM; non-extensive metabolizer (CYP2C19), S_{Cr}; serum creatinine, TB; total bilirubin.

Table 15 Multiple linear regression for K_m prediction

	Unstandardized coefficient		Standardized coefficient	t	p-value
	B	Standard error	Beta		
Constant	-1.907	0.925		-2.062	0.045
Age	0.042	0.014	0.388	3.095	0.003
TB	1.195	0.369	0.428	3.234	0.002
ALP	-0.003	0.001	-0.305	-2.307	0.026
Model adjusted R^2 = 0.262 (p = 0.001)					

Abbreviation: ALP; alkaline phosphatase, TB; total bilirubin.

Part B: Clinical outcome assessment and factors influencing clinical outcome

A total of 81 patients were included in clinical outcome assessment group. Forty (50.6%) of the patients were male, the median age of all patients was 56.1 y (range, 18.1–86.5 y), and the median weight at the start of the VRZ therapy was 56.1 kg (range, 38.8–82.0 kg). Sixty (74.1%) patients had hematologic malignancies. Forty-seven (58.0%) of patients were diagnose with probable IA with the most frequent source of infection was lung (N = 62, 82.7%). Considering the baseline liver function tests (LFTs), our patients had median ALP and GGT serum levels above the ULN values and a median albumin level lower than the normal value. Moreover, their median hemoglobin, hematocrit and platelet counts were lower than the normal ranges, while other laboratory tests were in the normal range. According to their CYP2C19 phenotype, 34 (47.9%) patients were extensive metabolizers, 31 (43.6%) patients were intermediate metabolizers and only 6 (8.4%) patients were poor metabolizers (Table 16).

Considering to voriconazole administration, most of patients (89.0%) received VRZ as oral dose with median loading dose of 12 mg/kg/day followed by median maintenance dose of 8 mg/kg/day. After VRZ initiation, blood samples were drawn for VRZ concentration measurement with median of 11.5 h after last dose administration on day 9 (range 3-164 d). For three patients with blood sampling before day 5, they all received VRZ loading doses, therefore, steady state was assumed after 24 h. The median initial, second, and third VRZ C_{tr} was 2.17 mg/L, 2.40 mg/L, and 2.34 mg/L which was not significant difference and were in the present recommended therapeutic range. The median sampling time was 103 d with median outcome evaluation on day 73. Overall success rate in this study was 76.5%. Among 19 patients with failure to response, 12 patients were dead due to any cause (mortality rate = 14.8%) as shown in Table 16. After excluded patient with possible IA (N = 64), demographic data of remaining patients was not different from all patients and treatment outcome was also comparable with overall success and mortality rate of 73.4% and 17.2%, respectively (Table 17).

Table 16 Demographic data and treatment outcome of individuals eligible for clinical outcome assessment (N = 81)

Characteristics	Data
Age – median, years (range)	54.6 (18.1-86.5)
Gender, male (%)	40 (49.4)
female (%)	41 (50.6)
Weight – median, kg (range)	56.1 (38.8-82.0)
Underlying condition – number (%)	
Hematologic malignancy	60 (74.1)
Solid tumor	4 (4.9)
Immunosuppressive Therapy	9 (11.1)
HIV/AIDS	2 (2.5)
Other condition	2 (2.5)
None	4 (4.9)
Fungal Infection – number (%)	
Proven	17 (21.0)
Probable	47 (58.0)
Possible	17 (21.0)
Source of infection – number (%)	
Lung	67 (82.7)
Sinus	13 (16.0)
Disseminated	1 (1.2)
Baseline laboratory tests (normal range) [a]	Median (IQR)
S_{Cr} (0.4-1.2 mg/dL)	0.91 (0.55)
Cl_{Cr} (mL/min)	70.0 (45.8)
AST (15-37 U/L)	35 (28)
ALT (30-65 U/L)	43 (44)
ALP (50-136 U/L)	160 (187)
GGT (male: 15-85 U/L, female 5-55 U/L)	319 (418), 258 (337)
TB (0.2-1.2 mg/dL)	0.7 (0.6)
DB (0.0-0.3 mg/dL)	0.3 (0.4)
Albumin (35-50 g/L)	28.3 (11.3)

Table 16. (cont.) Demographic data and treatment outcome of individuals eligible for clinical outcome assessment (N = 81)

Characteristics	Data
Baseline laboratory tests (normal range) [a]	Median (IQR)
WBC (4,000-10,700 cells/cm^3)	5,745 (6,690)
% N (40%-74%)	70 (33)
ANC (1,500-8,000 cells/mm^3)	3,781 (4,917)
Hb (male: 14.0-17.5 g/dL	10.2 (2.0)
female: 12.0-16.0 g/dL)	9.4 (1.9)
Hct (male: 40%-54%	30.1 (6.2)
female: 36%-48%)	29.2 (6.0)
Plt (140-450 x10^3/mm^3)	129 (118)
CYP2C19 phenotypes and genotypes (N=71) – number (%)	
EM (N = 34, 47.9%)	
*1/*1	34 (47.9)
IM (N = 31, 43.6%)	
*1/*2	26 (36.6)
*1/*3	5 (7.0)
PM (N = 6, 8.4%)	
*2/*2	4 (5.6)
*2/*3	1 (1.4)
*3/*3	1 (1.4)
Route of administration – number (%)	
Switch from intravenous to oral	17 (21.0)
Oral	64 (89.0)
Voriconazole daily dosing – median, mg/kg/day (range)	
Loading dose (oral or intravenous)	12
Maintenance dose	8 (5.3-9.8)
No. of samples per patient – median, number (range)	3 (1–18)
Days from the start of therapy to sampling – median, days (range)	9 (3-164)
Hours between last dose and trough drug level – median, hours (range)	11.5 (9-14)

Table 16. (cont.) Demographic data and treatment outcome of individuals iligeble for clinical outcome assessment (N = 81)

Characteristics	Data
Voriconazole level – median, mg/L (range)	
Initial level (N=81)	2.17 (0.11-12.40)
Second level (N=67)	2.40 (0.52-9.71)
Third level (N=55)	2.34 (0.17-10.17)
Duration of therapy – median, days (range)	103 (8-655)
Duration of outcome evaluation – median, days (range)	73 (7-341)
Treatment outcome – number (%)	
Success	62 (76.5)
Complete response	13 (16.0)
Partial response	49 (60.5)
Failure – number (%)	19 (23.5)
Stable response	3 (3.7)
Progression of fungal disease	4 (4.9)
Dead due to any causes	12 (14.8)

[a]Reference data from clinical pathology laboratory, Ramathibodi hospital, Bangkok, Thailand.

Abbreviation: Alb: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; Cl_{Cr}: creatinine clearance; DB: direct bilirubin; EM: extensive metabolizer; GGT: γ-glutamyl transpeptidase; Hb: hemoglobin; Hct: hematocrit; IM: intermediate metabolizer; Plt: platelet; PM: poor metabolizer; S_{Cr}: serum creatinine; TB: total bilirubin.

Table 17 Demographic data and treatment outcome of individuals eligible for clinical outcome assessment excluding for possible IA (N= 64)

Characteristics	Data
Age – median, years (range)	56.1 (26.8)
Gender, male (%)	33 (51.6)
female (%)	31 (48.4)
Weight – median kg (range)	56.7 (13.2)
Underlying condition, number (%)	
Hematologic malignancy	47 (73.4)
Solid tumor	4 (6.3)
Immunosuppressive Therapy	8 (12.5)
HIV/AIDS	1 (1.6)
Other condition	2 (3.1)
None	2 (3.1)
Fungal Infection – number (%)	
Proven	17 (26.6)
Probable	47 (73.4)
Source of infection – number (%)	
Lung	54 (84.4)
Sinus	9 (14.1)
Disseminated	1 (1.6)
Baseline laboratory tests (normal range) [a]	Median (IQR)
S_{Cr} (0.4-1.2 mg/dL)	0.88 (0.56)
Cl_{Cr} (mL/min)	64.95 (46.46)
AST (15-37 U/L)	35 (29)
ALT (30-65 U/L)	43 (43)
ALP (50-136 U/L)	161 (191)
GGT (male: 15-85 U/L,	317 (422)
female 5-55 U/L)	258 (352)
TB (0.2-1.2 mg/dL)	0.7 (0.6)
DB (0.0-0.3 mg/dL)	0.3 (0.4)
Albumin (35-50 g/L)	27.6 (11.1)

Table 17. (cont.) Demographic data and treatment outcome of individuals eligible for clinical outcome assessment excluding for possible IA (N= 64)

Characteristics	Data
Baseline laboratory tests (normal range) [a]	Median (IQR)
WBC (4,000-10,700 cells/cm^3)	5,965 (6,755)
% N (40%-74%)	71 (33)
ANC (1,500-8,000 cells/mm^3)	4,026 (4,120)
Hb (male: 14.0-17.5 g/dL	10.4 (2.4)
female: 12.0-16.0 g/dL)	9.3 (2.1)
Hct (male: 40%-54%	30.2 (6.8)
female: 36%-48%)	28.5 (6.8)
Plt (140-450 x10^3/mm^3)	129 (118)
CYP2C19 phenotypes and genotype (N=56)	
EM (N = 28, 50%)	
*1/*1	28 (50)
IM (N = 23, 41.1%)	
*1/*2	19 (33.9)
*1/*3	4 (7.1)
PM (N = 5, 8.9%)	
*2/*2	3 (5.4)
*2/*3	1 (1.8)
*3/*3	1 (1.8)
Voriconazole daily dosing – median, mg/kg/day (range)	
Loading dose (oral or intravenous)	6
Maintenance dose	8 (5.3-9.8)
Duration of therapy – median, days (range)	100 (8-655)
Duration of outcome evaluation – median, days (range)	80 (7-341)

Table 17. (cont.) Demographic data and treatment outcome of individuals eligible for clinical outcome assessment excluding for possible IA (N= 64)

Treatment outcome – number (%)	
Success	47 (73.4)
Complete response	7 (10.9)
Partial response	40 (62.5)
Failure	17 (26.6)
Stable response	3 (4.7)
Progression of fungal disease	3 (4.7)
Dead due to any cause	11 (17.2)

[a]Reference data from clinical pathology laboratory, Ramathibodi hospital, Bangkok, Thailand.

Abbreviation: Alb: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; Cl_{Cr}: creatinine clearance; DB: direct bilirubin; EM: extensive metabolizer; GGT: γ-glutamyl transpeptidase; Hb: hemoglobin; Hct: hematocrit; IM: intermediate metabolizer; Plt: platelet; PM: poor metabolizer; S_{Cr}: serum creatinine; TB: total bilirubin.

Considering the effect of site of infection on success rate and duration of treatment, when maintain similar VRZ C_{tr}, aspergillus lung infection seem to had higher success rate (p = 0.0016) and require the shorter duration of treatment when compare to sinus infection (Table 18).

There were nineteen patients fail to response to voriconazole treatment. Eleven patients were male and only three patients were aged over than 65 y. Most of them (17/19 cases) were diagnosed as probable or proven IA. Of all, twelve patients were dead and among 12 dead cases, inavasive aspergillosis was supposed to be the cause of death in 4 cases. Table 19 showed the description of patients who had failure to treatment.

Table 18 Comparison of VRZ level, treatment outcome, and duration of treatment between *Aspergillus* lung and sinus infection (N = 80)

	Lung (N=67)[a]	Sinus (N=13)[a]	p-value
VRZ level (mg/L)			
median ± IQR (range)	2.74 ± 2.08 (0.56-8.20)	2.51±0.96 (1.33-4.13)	0.917
Success treatment, number (%)	58 (86.6)	10 (76.9)	0.0016*
Duration of treatment (d)			
median ± IQR (range)	104 ± 99 (33 -363)	282 ± 557 (46-655)	0.013*

[a]exclude one patient who had disseminated aspergillosis

Table 19 Descriptions of patients who failure to the treatment (N =19)

Pt. no.	Patient characteristic		Duration of VRZ treatment (d)	Treatment outcome
	Gender, age and UD	IA diagnosis and source of infection		
4	F 67 y HIV/AIDS	Probable IPA	12	Dead due to septic shock
16	M 22 y Hematologic malignancy	Proven IA sinusitis	86	Stable response then FESS
17*	M 38 y Hematologic malignancy	Proven IPA	42	Dead due to sudden cardiac death
26	M 33 y Hematologic malignancy	Probable IPA	51	Progression of fungal disease then switch to amphotericin B
45	F 29 y Immunosuppressive therapy	Probable IPA	56	Dead - Pneumonia due to other gram negative bacilli
48	F 63 y Hematologic malignancy	Probable IPA	111	Dead due to bacterial pneumonia
50	F 58 y Hematologic malignancy	Probable IPA	9	Dead due to ARDS
55	F 80 y Hematologic malignancy	Possible IPA	193	Dead due to IPA
60*	M 63 y Hematologic malignancy	Probable IPA	9	Dead due to IPA, CA lung, pneumonia
62	M 65 y Solid tumor (lung)	Probable IPA	12	Dead due to IPA, CA lung, pneumonia
68	M 57 y Hematologic malignancy	Possible IA sinusitis	123	Progression of disease then FESS
71*	F 45 y Immunosuppressive therapy	Probable IPA	26	Stable – continue VRZ
74	M 54 y HIV	Proven IA sinusitis	64	Stable then Lt. middle turbinectomy

Table 19. (cont.) Descriptions of patients who failure to the treatment (N =19)

Pt. no.	Patient characteristic		Duration of VRZ treatment (d)	Treatment outcome
	Gender, age and UD	IA diagnosis and source of infection		
80	M 57 y Hematologic malignancy	Proven IPA	23	Progression of disease then switch to Amphotericin B + Caspofungin
81*	M 67 y Immunosuppressive therapy	Probable IPA	16	Dead due to septic shock
84	M 82 y Hematologic malignancy	Probable IPA	45	Dead due to *S. aureus* septicemia
87	M 55 y Hematologic malignancy	Probable IPA	59	Dead due to septicemia
92	F 46 y Hematologic malignancy	Probable IPA	95	Treatment termination; end of life care
99	F 72 y Hematologic malignancy	Probable IPA	64	Dead due to disseminated Aspergillosis

*also developed drug-induced liver injury.

ARDS; Acute Respiratory Distress Syndrome, CA; cancer, F; female, FESS; Functional Endoscopic Sinus Surgery, HIV; human immunodeficiency virus, IA; invasive aspergillosis, IPA; invasive pulmonary aspergillosis; M; male, UD; underlying disease(s).

Regarding to correlation between VRZ C_{tr} and treatment success, we found the success rate of more than 90% with VRZ C_{tr} of 4 mg/L and more than 95% with VRZ C_{tr} of 5 mg/L. This finding indicated that the optimal VRZ C_{tr} for IA treatment success should be ranging from 3 to 4 mg/L, but for level of 4-5 mg/L, the success rate increase only 4.9% (Table 20).

Table 20 Number of patients with success response stratified by voriconazole trough concentrations (N=62)

VRZ C_{trough}	Number of patients	% success	Cumulative % success
< 1	6	9.7	9.7
≥ 1-2	19	30.6	40.3
> 2-3	16	25.8	66.1
> 3-4	15	24.2	90.3
> 4-5	3	4.9	95.2
> 5	3	4.8	100.0
Level of patients with success response, median ± IQR (range) = 2.48±1.75 (0.56-8.20)			

With respect to adverse side effects, hepatotoxicity or drug-induced liver injury (DILI) was the only adverse effect observed during this study. Hepatotoxicity developed in 11 (13.6%) patients which the description of the patients, VRZ dose and level, the abnormal LFT, and treatment outcome were shown in Table 21. Seven (63.6%) patients were male, only one patient aged over than 65 y, and 4 (40%) were *CYP2C19 *1/*2* genotype while the remaining were *CYP2C19 *1/*1* genotype. Three patients had chronic HBV or HCV infection and one patient had alcoholic cirrhosis of liver. Onset of DILI was ranging from 5 to 326 d after VRZ initiation. The dose of VRZ that caused DILI ranging from 400 mg to 600 mg daily with VRZ C_{tr} of 0.63-10.17 mg/L. The last VRZ C_{tr} previous to the onset of DILI was 2.50-12.30 mg/L (range 5-97 d before the onset of DILI). DILI did not seem to correlate with treatment response because 8/11 patients who developed DILI had success treatment (Table 21).

To search out the relationship between VRZ C_{tr} and DILI, patients were stratified by VRZ C_{tr}. We found that the rate of DILI increased sharply with VRZ C_{tr} of more than 5 mg/L for both VRZ C_{tr} at the onset of DILI and the last VRZ C_{tr} previous to the onset of DILI (Table 22).

Table 21 Characteristics, VRZ dosage description, hepatic investigation, and treatment outcome of patients who developed DILI (N = 11)

	Patient characteristic		VRZ regimen (level, mg/L)			
Pt. no.	Gender, age and CYP 2C19	Underlying disease	TTT	TTT-1	Hepatic investigation	Treatment outcome
17	M 38 y *1/*2 (IM)	- hematologic malignancy - chronic HBV and HCV	d41, 200 mg bid (10.17)	d26, 200 mg bid (4.67)	TB 2.5x	Dead due to sudden cardiac death
25	M 50 y *1/*2 (IM)	- Hematologic malignancy - Chronic HBV	d326, 250 mg bid (5.10)	d229, 300 mg bid (5.30)	TB 3.17x	Success - partial response
60	M 63 y	- Hematologic malignancy	d5, 200 mg bid (7.48)	-	TB 3.25x	Dead due to septicemia
71	F 50 y *1/*1 (EM)	- Immunosuppressive therapy - Chronic HBV	d37, 250 mg bid (6.31)	d16, 250 mg bid (5.74)	TB 2.08x	Failure- stable response
72	M 59 y *1/*1 (EM)	- Solid tumor (lung - Alcoholic cirrhosis of liver	d25, 200 mg bid (3.23)	d12, 200 mg bid (3.12)	TB 5.92x	Success- partial response
79	F 44 y *1/*2 (IM)	- Hematologic malignancy	d9, 200 mg bid (0.63)	-	ALT 5.78x	Success- partial response
81	M 67 y *1/*1 (EM)	- Immunosuppressant therapy	d11, 250 mg bid (2.73)	d6, 250 mg bid (4.99)	TB 2.50x	Success- partial response
91	M 39 y *1/*2 (IM)	- Hematologic malignancy	d40, 300 mg bid (6.58)	d32, 300 mg bid (2.50)	ALT 11.40x	Success- partial response

Table 21. (cont.) Characteristics, VRZ dosage description, hepatic investigation, and treatment outcome of patients who developed DILI

Pt. no.	Patient characteristic: Gender, age and CYP 2C19	Patient characteristic: Underlying disease	VRZ regimen (level, mg/L): TTT	VRZ regimen (level, mg/L): TTT-1	Hepatic investigation	Treatment outcome
93	M 37 y *1/*1 (EM)	- Hematologic malignancy	d76, 250 mg bid (1.56)	d59, 250 mg bid (4.29)	TB 2.83x	Success- partial response
105	F 35 y *1/*1 (EM)	- Immunosuppressive therapy	d80, 250 mg /200 mg (2.21)	d64, 250 mg /200 mg (5.10)	ALT 13.20x	Success- partial response
106	F 38 y *1/*1 (EM)	- Hematologic malignancy - Chronic HBV	d83, 250 mg /200 mg (4.00)	d72, 250 mg bid (12.30)	TB 4.58x	Success- partial response

DILI; drug-induced liver injury, HBV; hepatitis B virus, HCV; hepatitis C virus, TTT; time to toxicity, TTT-1, the last investigation previous to TTT.

Table 22 Number of patient with DILI stratified by voriconazole trough concentrations (N = 11)

DILI (N =11)		DILI-1 (N = 9)	
VRZ C_{tr}	Number of patients (%)	VRZ C_{tr}	Number of patients (%)
< 1	1 (9.1)	< 1	0
≥ 1-2	1 (9.1)	≥ 1-2	0
> 2-3	1 (9.1)	> 2-3	2 (22.2)
> 3-4	1 (9.1)	> 3-4	1 (11.1)
> 4-5	2 (18.2)	> 4-5	2 (22.2)
> 5	5 (45.5)	> 5	4 (44.4)

DILI; drug-induced liver injury, DILI VRZ C_{tr} were the level between 0-14 d before DILI occur, DILI-1; indicated the last investigation previous to DILI occurred.

DISCUSSION

The calculated K_m for the EM group was lower than that in the non-EM group, which was reasonable because the lower K_m was related to the higher VRZ metabolizing activity. Although the baseline liver function test (LFT), as in the serum ALT level, of the EM group were worse than the non-EM group, the K_m of the EM group still was lower than that of the non-EM group. The median K_m for all our patients was 0.391 mg/L, which was 3.38-fold lower than that reported previously (1.32 mg/L), although this may reflect the higher frequency of CYP2C19 EM in our study compared to that in the Japanese population (43). Another factor that could possibly explain the low value of our patient's K_m was the low frequency of the *CYP2C19*17* gain of function allele in the Asian population of this study. Besides CYP2C19, CYP3A4 was also responsible for VRZ metabolism and so CYP3A4 polymorphism could play a role as well. However, CYP3A4 variants were not determined in this study and so their effects on the VRZ K_m and V_{max} in our patients were unknown.

With respect to the calculated V_{max}, it was not much different between the patients in this study and that in previous studies based upon populations as Matsumoto, Hope and Dalton's groups (30, 67, 72), suggesting the maximum rate of VRZ metabolism was not significantly different between different ethnic groups.

When the patients' factors were studied for the effect on the K_m and V_{max} of VRZ, we found that other than the liver function (ALT), the renal function (S_{Cr} and Cl_{Cr}) also influenced the K_m, while only S_{Cr} affected the patient's V_{max}. It was known that VRZ was mainly eliminated by liver metabolism, with excretion unchanged by the kidneys accounting for only 2%. For our patients who had abnormal baseline LFTs, the kidneys might have had a significant role in VRZ elimination.

The recommended VRZ doses derived in this study were not equal to those in the VRZ package insert, which recommended a daily dose of 12 mg/kg/d for 1 d as a loading dose followed by 8 mg/kg/d as a maintenance dose for adult patients. Based on our calculations, if the EM individuals received the VRZ dose recommended in the

package insert, their VRZ plasma C_{tr} would be lower than 1 mg/L, which was insufficient, although the IM or PM groups would maintain the VRZ plasma C_{tr} within the therapeutic range. Since CYP2C19 EM was found in the majority of the Thai population, as well as Asian populations (25, 26, 73), then CYP2C19 polymorphisms were an important factor in determining the VRZ dosing levels to optimize the VRZ plasma C_{tr}.

The calculation of the K_m and V_{max} values had a high degree of uncertainty due to the fairly wide range of values compared to the median value. Furthermore, the median C_{tr} after receiving the same maintenance dose did not differ significantly between the EM and non-EM groups because those values also showed a wide range of variation, masking the reasonable trend. Thus, the initiation of VRZ treatment with our recommended dose followed by therapeutic drug monitoring was warranted.

The overall success rate in the present study (76.5%) was higher than that reported in previous studies (11, 61, 64), which was possibly due to the restricted VRZ use in our setting that has not yet selected for increased resistance of *Aspergillus* spp. to VRZ. Although the minimum inhibitory concentration (MIC) of VRZ for *Aspergillus* spp. was only determined in two cases (< 0.1 mg/L in both cases), these were lower than those reported in another study (74). In that study, more than 80% of the most frequent *Aspergillus* spp. (*A. fumigatus* (2778 isolates), *A. flavus* (589 isolates), *A. terrueus* (462 isolates) and *A. niger* (479 isolates)) had a VRZ MIC of > 0.125 mg/L and more than 50% of them had a VRZ MIC of > 0.25 mg/L (74). Therefore, for all our patients who had a median VRZ concentration of more than 0.5 mg/L, the drug levels were several-fold higher than the MIC value which were sufficient to control the pathogen, leading to the high success rate.

The blood sampling time varied over the diverse range of 9 to 16 h because there was no definitive VRZ administration protocol in our institution, especially for oral administration. Oral VRZ should be administered on an empty stomach which was 1 h before or 2 h after a meal, and so the VRZ administration times were adjusted to the patients' meal time. For example, breakfast and dinner time in our setting were 7 AM and 5 PM so the drug administration times were 6 AM and 4 PM. For monitoring the VRZ

C_{tr}, the blood samples were collected around 30 min before administration of the next VRZ dose, and so the blood sampling time depended on the drug administration time. This could explain the high variation in VRZ concentrations.

This study found the association between VRZ C_{tr} and treatment success which was concordant with previous studies that found a significant relationship between treatment failure and VRZ concentrations of less than 1.7 mg/L was reported in patients with IFIs (60), while another study determined that the IFI-related mortality was correlated with an initial VRZ C_{tr} of $\leq$ 0.35 mg/L and success outcomes were more likely among patients with a median VRZ C_{tr} of more than 2.2 mg/L (61). Nevertheless, they also reported that patients with a median VRZ C_{tr} of 2.38 mg/L were more likely to face severe adverse effects than those with a median VRZ C_{tr} of 1.30 mg/L. In addition, in another study, the VRZ prophylaxis was reported to be most effective at a VRZ C_{tr} of > 1.5 mg/L in lung transplant recipients (75).

With respect to adverse side effects, only hepatotoxicity was observed in this study. We found the dramatically increased rate of hepatotoxicity with VRZ C_{tr} of more than 5 mg/L which was confirmed the previous finding that reported a correlation between the VRZ concentration and toxicity, where a higher rate of neurotoxicity was found when the VRZ C_{tr} was more than 5 mg/L (60), while the median VRZ concentrations were significantly higher in patients with severe adverse events (6.32 mg/L vs. 2.15 mg/L) (62). On the other hand, some studies could not elucidate a relationship between VRZ concentrations and adverse events (64, 65). In addition, this study's results indicated that DILI were associated with VRZ C_{tr} at the time of DILI and previous VRZ C_{tr} before DILI. This finding confirmed the result of Suzuki's study which reported that sustained high trough concentration of voriconazole may increase the risk of hepatotoxicity, and decreasing trough concentration to less than 4 mg/L by dose adjustment after the initial TDM may reduce the incidence of hepatotoxicity in patients treated with voriconazole (63).

The limitations of this study were the retrospective design, and that the VRZ plasma concentration assays were performed by two separate laboratories where inter-

laboratory variation might occur. In addition, since there were only five members of the PM group included in this study, we could not calculate the recommended dose for each phenotypic group (EM, IM and PM), which might be more optimal for each individual. Furthermore, the time after last administration dose to the blood sampling was varied depending on meal time, ranging from 9 to 14 h, VRZ C_{tr} then had high variation. Based on our findings, time to steady state were different between CYP2C19 phenotypes and also dose dependent, blood sampling on the same day, such as on day 5, for every patients may not be appropriated and monitoring two consecutive C_{tr} might be useful to comfirm steady state level. Therefore, further prospective studies with a relatively large number of patients with each CYP2C19 phenotype were needed. Because MICs of *Aspergillus* spp. were identified only two cases in this study, the correlation between MIC or C_{tr}/MIC and clinical outcome could not be determined.

In conclusion, we recommended starting VRZ treatment with the recommended doses followed by therapeutic drug monitoring to maintain VRZ C_{tr} of 3-4 mg/L to get the successful of IA treatment and to avoid hepatotoxicity.

CHAPTER V

CONCLUSIONS

The K_m of voriconazole for Thai adult patients were 0.26 mg/L and 0.67 mg/L for individuals with CYP2C19 EM and non-EM, respectively. The V_{max} of voriconazole were 0.43 mg/kg/h and 0.48 mg/kg/h for individuals with CYP2C19 EM and non-EM, respectively.

For Thai adult patients, invasive aspergillosis treatment by VRZ should be started with recommended loading dose of 12 mg/kg/d divided into two equal doses every 12 hours to expedite steady state. Maintenance dose should be based on CYP2C19 phenotype and followed by VRZ C_{trough} monitoring because of high variation in its pharmacokinetics. Our recommended doses for CYP2C19 EM and non-EM were approximate 10.3 mg/kg/d and 9.2 mg/kg/d divided into two equal doses every 12 hours, respectively, to maintain voriconazole trough concentration of around 3 mg/L. Based on our data, if our recommended doses were given, steady state levels would achieved on approximately 20 d and 17 d for EM and non-EM, without loading dose, respectively. Therefore, in individual who received loading dose, VRZ level would achieve steady state sooner and sampling time would be earlier than 20 d and 17 d, respectively. This finding also indicated the necessity of *CYP2C19* genotyping. In case of *CYP2C19* genotyping is not available, K_m for individual patient could be estimated by reported equation where age, TB, and ALP were the predictors for K_m and none of patient's factors could predict V_{max}, so the median V_{max} (0.47 mg/kg/h) was recommended. Then, the maintenance dose will be further calculated by Michaelis-Menten equation.

Since we found the high treatment success rate with VRZ C_{tr} of 3-4 mg/L and the dramatically increased hepatotoxicity rate with VRZ C_{tr} of more than 5 mg/L, we recommended maintaining VRZ C_{tr} within the range of 3-4 mg/L.

REFERENCES

1. Kontoyiannis DP, Patterson TF. Diagnosis and treatment of invasive fungal infections in the cancer patient: recent progress and ongoing questions. Clin Infect Dis. 2014;59(Suppl 5):S356–S9.
2. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813-21.
3. Drew RH, Townsend ML, Pound MW, Johnson SW, Perfect JR. Recent advances in the treatment of life-threatening, invasive fungal infections Expert Opin Pharmacother 2013;14(17):2361-74.
4. Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. Am J Med. 2012;125(1 Suppl):S1-S13.
5. Herbrecht R, Denning DW, Patterson TF, Bennett JE, GREENE RE, OESTMANN JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408-15.
6. Lass-Flörl C. Triazole antifungal agents in invasive fungal infections: a comparative review. Drugs. 2011;71(18):2405-19.
7. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents : pharmacokinetics, safety and efficacy. Drugs. 2004;64(18):1997-2020.
8. Muijsers RBR, Goa KL, J. SL. Voriconazole in the treatment of invasive aspergillosis. Drugs. 2002;62(18):2655-64.

9. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(3):327-60.

10. Johnson B, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis. 2003;36:630–7.

11. Scott LJ, Simpson D. Voriconazole: A review of its use in the management of invasive fungal infections. Drugs. 2007;67(2):269-98.

12. Ally R, Schürmann D, Kreisel W, Carosi G, Aguirrebengoa K, Dupont B, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis. 2001;33(9):1447-54.

13. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis. 2003;36:630-7.

14. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med. 2002;346:225-34.

15. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis. 2002;34:563-71.

16. Philips JA, Marty FM, Stone RM, Koplan BA, Katz JT, Baden LR. Torsades de pointes associated with voriconazole use. Transpl Infect Dis. 2007;9(1):33-6.

17. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 2008;46(2):201-11.

18. Lewis RE. What is the "therapeutic range" for voriconazole? Clin Infect Dis. 2008;46(2):212-4.

19. Zonios DI, Gea-Banacloche J, Childs R, Bennett JE. Hallucinations during voriconazole therapy. Clin Infect Dis. 2008;47(1):e7-e10.
20. Thompson GR, Lewis JS. Pharmacology and clinical use of voriconazole Expert Opin Drug Metab Toxicol. 2010;6(1):83-94.
21. Chayakulkeeree M, Poovipirom N, Siengwattana P, Maneerattanaporn M. Effect of proton pump inhibitor on plasma voriconazole concentration in Thai patients. J Med Assoc Thai. 2015;98(3):232-7.
22. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet. 2006;45(7):649-63R.
23. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother. 2002;46(8):2546-53.
24. Kurose K, Sugiyama E, Saito Y. Population differences in major functional polymorphisms of pharmacokinetics/pharmacodynamics-related genes in Eastern Asians and Europeans: implications in the clinical trials for novel drug development. Drug Metab Pharmacokinet. 2012;27(1):9-54.
25. Sukasem C, Tunthong R, Chamnanphon M, Santon S, Jantararoungtong T, Koomdee N, et al. CYP2C19 polymorphisms in the Thai population and the clinical response to clopidogrel in patients with atherothrombotic-risk factors. Pharmgenomics Pers Med. 2013;6:85-91.
26. Chuwongwattana S, Jantararoungtong T, Chitasombat MN, Puangpetch A, Prommas S, Dilokpattanamongkol P, et al. A prospective observational study of CYP2C19 polymorphisms and voriconazole plasma level in adult Thai patients with invasive aspergillosis. Drug Metab Pharmacokinet. 2016;31(2):117-22.
27. Lee S, Kim BH, Nam WS, Yoon SH, Cho JY, Shin SG, et al. Effect of CYP2C19 polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers. J Clin Pharmacol. 2012;52(2):195-203.

28. Li X, Yu C, Wang T, Chen K, Zhai S, Tang H. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2016;72(10):1185-93.
29. Wang T, Zhu H, Sun J, Cheng X, Xie J, Dong H, et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents. 2014;44(5):436-42.
30. Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. J Antimicrob Chemother. 2014;69(6):1633-41.
31. Hamadeh IS, Klinker KP, Borgert SJ, Richards AI, Li W, Mangal N, et al. Impact of the CYP2C19 genotype on voriconazole exposure in adults with invasive fungal infections. Pharmacogenet Genomics. 2017;27(5):190-6.
32. Sienkiewicz B, Urbaniak-Kujda D, Dybko J, Drys A, Hurkacz M, Wrobel T, et al. Influence of CYP2C19 genotypes on the occurrence of adverse drug reactions of voriconazole among hematological patients after allo-HSCT. Pathol Oncol Res. 2017.
33. Trubiano JA, Crowe A, Worth LJ, Thursky KA, Slavin MA. Putting CYP2C19 genotyping to the test: utility of pharmacogenomic evaluation in a voriconazole-treated haematology cohort. J Antimicrob Chemother. 2015;70(4):1161-5.
34. Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol. 2009;49(2):196-204.
35. Shi HY, Yan J, Zhu WH, Yang GP, Tan ZR, Wu WH, et al. Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. Eur J Clin Pharmacol. 2010;66(11):1131-6.

36. Narita A, Muramatsu H, Sakaguchi H, Doisaki S, Tanaka M, Hama A, et al. Correlation of CYP2C19 phenotype with voriconazole plasma concentration in children. J Pediatr Hematol Onco. 2013;35(5):e219-23.
37. Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol. 2009;65(3):281-5.
38. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther. 2004;75(6):587-8.
39. Lei HP, Wang G, Wang LS, Ou-yang DS, Chen H, Li Q, et al. Lack of effect of Ginkgo biloba on voriconazole pharmacokinetics in Chinese volunteers identified as CYP2C19 poor and extensive metabolizers. Ann Pharmacother. 2009;43(4).
40. Hassan A, Burhenne J, Riedel KD, Weiss J, Mikus G, Haefeli WE, et al. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. 2011;33:86–93. 2011;33:86-93.
41. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. Br J Clin Pharmacol. 2009;68(6):906-15.
42. Berge M, Guillemain R, Tregouet DA, Amrein C, Boussaud V, Chevalier P, et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol. 2011;67(3):253-60.
43. Obeng AO, Egelund EF, Alsultan A, Peloquin CA, Johnson JA. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? Pharmacotherapy. 2014;34(7):703-18.
44. Lamoureux F, Duflot T, Woillard JB, Metsu D, Pereira T, Compagnon P, et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure

in adult patients with invasive fungal infections. Int J Antimicrob Agents. 2016;47(2):124-31.

45. Teusink A, Vinks A, Zhang K, Davies S, Fukuda T, Lane A, et al. Genotype-directed dosing leads to optimized voriconazole levels in pediatric patients receiving hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2016;22(3):482-6.
46. Pfizer Inc. Label: voriconazole for injection, tablets, oral suspension: LAB-0271-12; 2005 Mar.
47. Li TY, Liu W, Chen K, Liang SY, Liu F. The influence of combination use of CYP450 inducers on the pharmacokinetics of voriconazole: a systematic review. J Clin Pharm Ther. 2017;42(2):135-46.
48. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R. Voriconazole therapeutic drug monitoring: focus on safety. Expert Opin Drug Saf. 2010;9(1):125-37.
49. Qi F, Zhu L, Li N, Ge T, Xu G, Liao S. Influence of different proton pump inhibitors on the pharmacokinetics of voriconazole. Int J Antimicrob Agents. 2017;49(4):403-9.
50. Yasu T, Konuma T, Kato S, Kurokawa Y, Takahashi S, Tojo A. Different effects of lansoprazole and rabeprazole on the plasma voriconazole trough levels in allogeneic hematopoietic cell transplant recipients. Ann Hematol. 2016;95(11):1845-51.
51. Purkins L, Wood N, Greenhalgh K, Eve MD, Oliver SD, Nichols D. The pharmacokinetics and safety of intravenous voriconazole - a novel wide-spectrum antifungal agent. British Journal of Clinical Pharmacology. 2003;56:2-9.
52. Driscoll TA, Frangoul H, Nemecek ER, Murphey DK, Yu LC, Blumer J, et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. Antimicrob Agents Chemother. 2011;55(12):5780-9.
53. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual

adverse events or liver function test abnormalities. J Clin Pharmacol. 2006;46(2):235-43.

54. Hoffman HL, Rathbun RC. Review of the safety and efficacy of voriconazole. Expert Opin Investig Drugs. 2002;11(3):409-29.

55. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother. 2011;55(6):2601-5.

56. Davies-Vorbrodt S, Ito JI, Tegtmeier BR, Dadwal SS, Kriengkauykiat J. Voriconazole serum concentrations in obese and overweight immunocompromised patients: a retrospective review. Pharmacotherapy 2013;33(1):22-30.

57. Koselke E, Kraft S, Smith J, Nagel J. Evaluation of the effect of obesity on voriconazole serum concentrations. J Antimicrob Chemother. 2012;67(12):2957-62.

58. Weiler S, Zoller H, Graziadei I, Vogel W, Bellmann-Weiler R, Joannidis M, et al. Altered pharmacokinetics of voriconazole in a patient with liver cirrhosis. Antimicrob Agents Chemother 2007;51(9):459-60.

59. Groll AH, Gea-Banacloche JC, Glasmacher A, Just-Nuebling G, Maschmeyer G, Walsh TJ. Clinical pharmacology of antifungal compounds. Infect Dis Clin North Am. 2003;17(1):159-91, ix.

60. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56(9):4793-9.

61. Miyakis S, J. van Hal S, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. Clin Microbiol Infect 2010;16:927-33.

62. Kim SH, Yim DS, Choi SM, Kwon JC, Han S, Lee DG, et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. Int J Infect Dis. 2011;15(11):e753-8.

63. Suzuki Y, Tokimatsu I, Sato Y, Kawasaki K, Sato Y, Goto T, et al. Association of sustained high plasma trough concentration of voriconazole with the incidence of hepatotoxicity. Clin Chim Acta. 2013;424:119-22.

64. Chu HY, Jain R, Xie H, Pottinger P, Fredricks DN. Access voriconazole therapeutic drug monitoring: retrospective cohort study of the relationship to clinical outcomes and adverse events. BMC Infect Dis. 2013;13(105).

65. Racil Z, Winterova J, Kouba M, Zak P, Malaskova L, Buresova L, et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. Mycoses. 2012;55(6):483-92.

66. Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother. 2006;50(4):1570-2.

67. Matsumoto K, Ikawa K, Abematsu K, Fukunaga N, Nishida K, Fukamizu T, et al. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. Int J Antimicrob Agents. 2009;34(1):91-4.

68. Ueda K, Nannya Y, Kumano K, Hangaishi A, Takahashi T, Imai Y, et al. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. Int J Hematol. 2009;89(5):592-9.

69. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother. 2011;55(10):4782-8.

70. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis. 2010;50(1):27-36.

71. Chughlay MF, Blockman M, Cohen K. A clinical approach to drug-induced liver injury. Curr All Clin Imm. 2015;28(4):252-6.

72. Hope WW. Population pharmacokinetics of voriconazole in adults. Antimicrob Agents Chemother. 2012;56(1):526-31.

73. Kimura M, Ieiri I, Mamiya K, Urae A, Higuchi S. Genetic Polymorphism of Cytochrome P450s, CYP2C19, and CYP2C9 in a Japanese Population. Therapeutic Drug Monitoring. 1998;20(3):243-7.

74. Xu G, Zhu L, Ge T, Liao S, Li N, Qi F. Pharmacokinetic/pharmacodynamic analysis of voriconazole against *Candida* spp. and *Aspergillus* spp. in children, adolescents and adults by Monte Carlo simulation. Int J Antimicrob Agents. 2016;47(6):439-45.

75. Mitsani D, Nguyen MH, Shields RK, Toyoda Y, Kwak EJ, Silveira FP, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother. 2012;56(5):2371-7.

APPENDIX

APPENDIX A

คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล
๒๗๐ ถนนพระราม ๖ แขวงทุ่งพญาไท เขตราชเทวี กทม. ๑๐๔๐๐
โทร. (๐๒) ๒๐๑-๑๐๐๐

Faculty of Medicine Ramathibodi Hospital, Mahidol University.
270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand
Tel. (662) 201-1000

Documentary Proof of Ethical Clearance
Committee on Human Rights Related to Research Involving Human Subjects
Faculty of Medicine Ramathibodi Hospital, Mahidol University

No MURA2014/375

Title of Project	Pharmacokinetic/pharmacodynamic Study of Voriconazole for Invasive Aspergillosis Treatment in Thai Adult Patients
Protocol Number	ID 07 – 57 – 21
Principal Investigator	Miss Montira Tantasawat
Official Address	Department of Pharmacy Practice Faculty of Pharmaceutical Science Chulalongkorn University

The aforementioned project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, based on the Declaration of Helsinki.

Signature of Secretary Committee on Human Rights Related to Research Involving Human Subjects	..... Prof. Duangrurdee Wattanasirichaigoon, M.D.
Signature of Chairman Committee on Human Rights Related to Research Involving Human Subjects	..... Prof. Pratak O-Prasertsawat, M.D.
Date of Approval	August 13 , 2014
Duration of Study	3 Years

APPENDIX B

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03
Published: June 14, 2010 (U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, National Cancer Institute)

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only;
intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct.					
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.					
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder.					
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall					

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self-care ADL	Moderate to severe encephalopathy; coma; life threatening consequence	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma.					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region.					

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system					
Portal vein thrombosis	-	Intervention not indicate	Medical intervention indicate	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

APPENDIX C

Ethical considerations

The process for obtaining participant informed consent will be in accordance with the Recruitment & Employment Confederation (REC) guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator and the participant shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant's medical notes together with a signed and dated note that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study activity will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

All study staff and investigators will endeavor to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. All source documents will be held securely, in a locked cabinet. Access to the information will be limited to investigators and any relevant regulatory authorities. Computer held data including the study database will be held securely and password protected. Information about the study in the participant's medical

records / hospital notes will be treated confidentially in the same way as all other confidential medical information. Electronic data will be backed up every month to local media. Any data used externally of the study stable will be anonymous.

APENDIX D

K_m, V_{max} and characteristics of individual patients in pharmacokinetic study

Pt. No.	Pt. ID	Gender	Age	CYP2C19 genotype	CYP2C19 phenotype	K_m (mg/L)	V_{max} (mg/L/h)
1	1	F	86.5	*1/*2	IM	1.19	0.41
2	3	F	57.2	*1/*2	IM	0.28	0.34
3	10	F	59.7	*1/*2	IM	0.22	0.48
4	12	M	66.4	*1/*2	IM	1.68	0.45
5	13	M	68.2	*1/*2	IM	2.94	0.63
6	14	M	18.0	*1/*1	EM	0.03	0.26
7	16	M	22.7	*1/*1	EM	0.05	0.41
8	20	M	82.3	*1/*2	IM	2.05	0.48
9	24	M	45.6	*1/*1	EM	0.09	0.40
10	25	M	50.1	*1/*2	IM	0.59	0.51
11	28	M	32.5	*1/*1	EM	0.39	0.42
12	30	M	35.8	*1/*2	IM	0.33	0.64
13	31	M	60.1	*1/*2	IM	0.47	0.34
14	32	M	40.6	*1/*2	IM	0.88	0.73
15	37	F	52.7	*1/*1	EM	0.32	0.55
16	38	F	44.3	*1/*1	EM	0.17	0.52
17	39	F	44.0	*1/*1	EM	0.48	0.56
18	44	F	47.2	*1/*2	IM	0.01	0.40
19	46	F	32.9	*1/*2	IM	2.90	0.79
20	47	F	59.2	*1/*1	EM	7.06	0.66
21	48	F	63.9	*2/*2	PM	1.20	0.64
22	49	F	61.2	*1/*1	EM	1.10	0.37
23	52	F	75.7	*1/*1	EM	0.03	0.33
24	55	F	80.0	*1/*2	IM	0.29	0.64
25	64	M	32.3	*1/*2	IM	0.27	0.34
26	65	F	27.5	*1/*2	IM	0.69	0.73

Pt. No.	Pt. ID	Gender	Age	CYP2C19 genotype	CYP2C19 phenotype	K_m (mg/L)	V_{max} (mg/kg/h)
27	66	M	65.7	*1/*1	EM	0.21	0.47
28	67	M	74.5	*1/*1	EM	0.27	0.43
29	68	M	57.6	*1/*2	IM	4.67	0.69
30	69	M	36.5	*1/*1	EM	0.13	0.42
31	72	M	59.8	*1/*1	EM	2.33	0.56
32	73	M	68.6	*2/*3	PM	0.45	0.33
33	74	M	54.5	*1/*2	IM	2.98	0.46
34	75	F	53.4	*1/*2	IM	0.67	0.69
35	77	M	52.0	*1/*2	IM	0.05	0.33
36	79	F	44.6	*1/*2	IM	0.04	0.43
37	80	M	57.4	*1/*1	EM	0.14	0.41
38	82	F	31.7	*1/*1	EM	0.01	0.32
39	84	M	82.5	*3/*3	PM	8.60	0.77
40	86	M	50.4	*1/*1	EM	0.14	0.49
41	87	M	54.6	*1/*1	EM	0.19	0.52
42	89	M	53.6	*1/*1	EM	0.42	0.42
43	90	F	44.9	*2/*3	PM	0.02	0.41
44	91	M	38.8	*1/*1	EM	0.26	0.61
45	92	F	46.3	*1/*1	EM	0.39	0.35
46	93	M	37.0	*1/*1	EM	0.51	0.51
47	94	F	74.0	*1/*1	EM	0.86	0.79
48	95	F	62.8	*2/*2	PM	1.03	0.49
49	97	M	44.1	*1/*1	EM	0.27	0.42
50	98	F	58.9	*1/*2	IM	2.86	0.55
51	102	M	54.5	*1/*2	IM	0.61	0.39
52	105	F	36.0	*1/*1	EM	0.23	0.53
53	106	F	38.5	*1/*1	EM	0.28	0.34

APPENDIX E

Case record form

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□ SCREENING	
Date □□/□□/2 0 □□		
1. เกณฑ์ในการคัดเลือกเข้ามาศึกษา (Inclusion Criteria)		
เกณฑ์	ใช่	ไม่ใช่
1. อายุมากกว่า 18 ปีขึ้นไป	□	□
2. ได้รับการวินิจฉัยว่าเป็น Invasive Aspergillosis	□	□
3. ได้รับการรักษาด้วยยา Voriconazole	□	□
4. ผู้ป่วยหรือญาติสามารถให้คำยินยอมเป็นลายลักษณ์อักษรได้	□	□
2. เกณฑ์ในการคัดออก (Exclusion Criteria)		
เกณฑ์	ใช่	ไม่ใช่
1. เป็นโรคตับขั้นรุนแรง (CTCAE ≥ 4)	□	□
2. เป็นสตรีมีครรภ์หรือมีแนวโน้มที่จะตั้งครรภ์ระหว่างการรักษา	□	□
3. แพทย์มีความเห็นว่าผู้ป่วยไม่ควรเข้าร่วมการศึกษา	□	□
3. จากเกณฑ์ในการคัดเลือกเข้ามาศึกษาดังกล่าวข้างต้นสรุปว่าผู้ป่วยมีลักษณะตรงตามเกณฑ์และมีคุณสมบัติเหมาะสมสำหรับเข้าสู่การศึกษาวิจัย □ 1.ใช่ □ 2. ไม่ใช่		
Page 1/10		

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□ SCREENING
Data collection date □□/□□/2 0 □□ อาสาสมัครลงนามยินยอมในแบบยินยอมอาสาสมัคร ICF □ 1. Yes □ 2. No	
Ward of admission	
PART A: ข้อมูลทั่วไปของผู้ป่วย	
1. อายุครบ □□ ปี (DOB □□/□□/□□)	2. เพศ □1. ชาย □2. หญิง

3. วันที่ลงวินิจฉัยว่าเป็น Invasive Aspergillosis (IA) □□/□□/ 2 0 □□

3.1 สิ่งตรวจพบ

□ Microbiology Date □□/□□/ 2 0 □□

Specimen.....

Finding.....

MIC.....

□ Radiology (CT scan) Date □□/□□/ 2 0 □□

Finding.....

□ Galactomannan index Date □□/□□/ 2 0 □□

Specimen.....

Value.....

3.2 Clinical findings reveal IA

□ Yes (specify).....

□ No

3.3 ผลการวินิจฉัย

□ Proven IA □ Probable IA □ Possible IA

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□ SCREENING
4. Underlying diseases (specify) 4.1..... 4.2..... 4.3..... 4.4..... 4.5.....	
Vital sign	
5. Temperature □□.□ centrigrade	6. Pulse Rate □□□ beats/minute
7. Body Weight □□□.□ kgs	8. Height □□□.□ cms
9. Blood Pressure □□□/□□ mmHg	
10. Allergy	
PART B : Lab analysis (BASELINE)	
1. Chemistry Sample collection date □□/□□/20□□	
1.1 SCr □□.□ mg/dL	1.2 eGRF □□□.□ mL/min
1.3 AST □□□ units	1.4 ALT □□□ units
1.5 GGT □□□□.□	1.6 Total bilirubin □□.□ mg/dL
1.7 Alkaline phosphatase □□□.□ mg/dL	1.8 Serum albumin □□.□ g/dL
Page 3/10	

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□ SCREENING
2. CBC Sample collection date □□/□□/20□□	
2.1 WBC □□□□.□ cells/mm^3	2.2 % Neutrophil □□.□ %
2.3 ANC □□□□.□ cells/mm^3	2.4 Platelet □□□.□ x $10^3/mm^3$
2.5 Hb □□.□ g/dL	2.6 Hct □□.□ %
Page 4/10	

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□

PART C: Voriconazole dosage regimen and plasmaconcentrations

Weight □□□.□ kg

1. Loading dose

1.1 □ Yes □ No

1.2 Start date □□/□□/20□□ Time □□.□□

1.2 Route □ IV □ PO

1.3 Dose □□□ mg q 12 h

1.4 Dose/wt □□.□ mg/kg q 12 h

1.5 Number of dose □□ doses

2. Maintenance dose

Dose ที่	Route		Dose		Date	Time
	IV	PO	mg q 12 h	mg/kg q 12 h		
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□
□	□	□	□□□	□.□□	□□/□□/20□□	□□.□□

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO ☐☐☐☐ PATEINT INITIALS ☐☐☐

PART C: Voriconazole dosage regimen and plasmaconcentrations

2. Maintenance dose (cont.)

Dose ที่	Route		Dose (mg) q 12 h	Dose (mg/kg)	Date	Time
	IV	PO				
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐
☐	☐	☐	☐☐☐	☐.☐☐	☐☐/☐☐/20☐☐	☐☐.☐☐

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients				PATEINT NO □□□□ PATEINT INITIALS □□□	
PART C: Voriconazole dosage regimen and plasmaconcentrations					
3. Blood collection					
Drug administration Date □□/□□/20□□ Time □□.□□					
Sample	Estimate sampling time		Actual sampling time	Time after dosing (min)	Level (mg/L)
	Date	TIme			
1 (0 h)	□□/□□	□□.□□	□□.□□	□□□	□□.□□
2 (1 h)	□□/□□	□□.□□	□□.□□	□□□	□□.□□
3 (2 h)	□□/□□	□□.□□	□□.□□	□□□	□□.□□
4 (4 h)	□□/□□	□□.□□	□□.□□	□□□	□□.□□
5 (12 h)	□□/□□	□□.□□	□□.□□	□□□	□□.□□
Page 7/10					

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□

PART E: Pharmacogenetics and Galactomannan Index

1. CYP2C19 polymorphism

Sample Collection Date □□/□□/20□□ Report Date □□/□□/20□□

Result □ Homozygous Extensive Metabolizer (EM, *1/*1)

□ Heterozygous Extensive Metabolizer (HEM; □*1/*2 □*1/*3)

□ Poor Metabolizer (PM; □*2/*2 □ *3/*3 □ *2/*3)

2. Galactomannan Index (GMI)

No.	Date	Day	Specimen		Result		
			Serum	BAL	Level	Positive	Negative
1 (Baseline)	□□/□□/20□□		□	□	□□.□	□	□
2	□□/□□/20□□	3	□	□	□□.□	□	□
3	□□/□□/20□□	7	□	□	□□.□	□	□
4	□□/□□/20□□	10	□	□	□□.□	□	□
5	□□/□□/20□□	14	□	□	□□.□	□	□

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO ☐☐☐☐ PATEINT INITIALS ☐☐☐

PART F : ADVERSE EVENTS

Adverse Event ☐1. No

☐ 2. Yes (specify) .....

.....

.....

.....

PART G: Clinical outcome

1. Date of evaluation ☐☐/☐☐/20☐☐ (…….....days after voriconazole initiation)

2. Total ☐☐☐ days of voriconazole treatment

3. Clinical outcome

☐ Success

❍ Complete response ❍ Partial response

☐ Failure

❍ Stable response ❍ Progression of fungal disease

☐ Non-evaluable

Case Record Form Pharmacokinetic/pharmacodynamic study of voriconazole for invasive aspergillosis treatment in Thai adult patients	PATEINT NO □□□□ PATEINT INITIALS □□□

ชนิดและขนาดของยาที่ใช้ล่าสุด

Medication	Started date	Stopped date	Route	Dose	Unit	Freq
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□
	□□/□□/20□□	□□/□□/20□□	□□	□□□.□	□□	□□

วันที่ลงบันทึก : □□/□□/20□□ Page 10/10

VITA

Montira Tantasawat was born in Bangkok, Thailand, on June 28th 1977. She received Bachelor of Science in Pharmacy degree in 1999 from the Faculty of Pharmaceutical Science, Chulalongkorn University, Thailand. She received Master of Science in Pharmacy degree (Clinical Pharmacy) in 2005 from Faculty of Pharmacy, Mahidol University, Thailand.