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A pharmacokinetic/pharmacodynamic analysis of a standard voriconazole regimen in different CYP2C19 genotypes by Monte Carlo simulation

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Objectives: The objective of this study was to evaluate the standard voriconazole dosage regimen (maintenance dose was 200 mg bid orally) against *Aspergillus* infections in different CYP2C19 genotypes from a pharmacokinetic/pharmacodynamic (PK/PD) perspective. Method: Monte Carlo simulation (MCS) was applied to simulate 5,000 patients by integrating published pharmacokinetic (PK) parameters, variability of PK parameters on CYP2C19 genotypes and microbiological data. *Results*: The standard dosage regimen for poor metabolizers (PM) with *Aspergillus* infections was effective except *A.versicolor*; for heterozygous extensive metabolizers (HEM), *Aspergillus fumigatus*, *A.terreus* and *A.nidulans* infections could be treated effectively with the standard dosage regimen; for extensive metabolizers (EM), the standard voriconazole dosage regimen failed to achieve the best outcome for the six *Aspergillus spp.* Increasing dose (e.g. 300 mg bid) or even changing the antifungal drug was needed for EM and most HEM patients with *Aspergillus* infection. *Conclusion*: Instead of using a standard dosage regimen for all patients, the voriconazole dosage regimen needs to be optimized for patients with different CYP2C19 genotypes.

1. Introduction

Voriconazole is a broad-spectrum antifungal agent showing *in vitro* activity against *Aspergillus spp.*, including itraconazole- and amphotericin B-resistant *Aspergillus fumigatus*, and emerging pathogens such as *Scedosporium spp.*and *Fusarium sp*p (Herbrecht 2004). It is used as initial treatment for immunocompromised patients with invasive aspergillosis giving higher survival rates compared with initial therapy with amphotericin B (Herbrecht et al. 2002).

However, voriconazole resistance has now been reported in most countries including Canada, India, China, and the United States (Howard SJ, Arendrup MC 2011). Approximately 300000 people are estimated to develop invasive aspergillosis annually, 1.5%-10% of the millions of highly immunocompromised patients at risk worldwide (Brown et al. 2012). Voriconazole resistance is particularly problematic for these patients, as it is accepted as first-line therapy. In addition, since voriconazole is mainly metabolized *via* the hepatic cytochrome P450 isoenzyme CYP2C19, which exhibits genetic polymorphisms (Goldstein 2001), voriconazole PK is substantially influenced by the CYP2C19 genotype (Mikus et al. 2006; Ikeda et al. 2004; Rengelshausen et al. 2005). Thus, only one standard dosage regimen against a wide range of aspergillosis infections with variable minimum inhibitory concentrations (MIC) in different CYP2C19 genotypes may be ineffective and lead to further increase in voriconazole resistance. The current standard dosage regimen is 400 mg twice a day on the first day and 200 mg twice a day on the following days in adults weighing $\geq$ 40 kg.

Therefore, a pharmacokinetic/pharmacodynamic (PK/PD) evaluation of the efficacy of the standard voriconazole dosage regimen for *Aspergillus* infections in different CYP2C19 genotypes is needed. The Optimizing Pharmacodynamic Target Attainment using the Meropenem Yearly Susceptibility Test Information Collection Antibiogram (OPTAMA) program used Monte Carlo simulation (MCS) as a tool for determining dosage regimens and assisting in the selection of appropriate empirical antibiotic therapies at national, regional and institutional levels (Kuti and Nicolau 2005; Sun et al.2005). MCS was able to link MIC data with a pharmacokinetic profile to predict the probability of a certain therapeutic outcome, thereby improving antimicrobial effectiveness and the quality of patient care.

The aim of the study was to calculate the probability of attaining targeted pharmacodynamic exposure against six *Aspergillus spp.* with variable MICs from different CYP2C19 genotypes to evaluate the efficacy of the standard voriconazole dosage regimen from a PK/PD perspective. Based on this, we investigated whether the standard dosage regimen achieves effective treatment in different CYP2C19 genotypes.

2. Investigations and results

2.1. Pharmacokinetic parameters and microbiological information

The pharmacokinetic (PK) parameters of voriconazole in healthy volunteers with different CYP2C19 genotypes were obtained from a published study (Lee et al. 2012). The steady-state apparent clearance (CLss/F) data for a dose regimen of

Table 1: Frequency distribution of voriconazole MICs for six *Aspergillus spp*. from five laboratories

Species	n	MIC(mg/L)										
		0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	16	32
A.fumigatus	2778	0.04	0.58	4.43	42.94	39.27	10.48	1.40	0.61	0.25		
A.flavus	590		0.17	2.54	19.49	49.15	26.78	1.69				
A.terreus	462	0.43		5.19	21.43	46.97	22.94	2.17			0.22	0.65
A.niger	479	0.63	1.04	3.97	12.32	36.32	35.28	9.81	0.63			
A.nidulans	139	2.88	10.07	36.69	23.74	8.63	10.07	7.35		0.72		
A.versicolor	80	3.75	3.75	15	28.75	12.5	17.5	16.25			3.75	

200 mg every 12 h, the only PK parameter used in stochastic simulations, were 12.6 ± 6.5 L/h, 5.9 ± 3.5 L/h, 3.5 ± 0.9 L/h (mean $\pm$ CV %) for extensive metabolizers (EM), heterozygous EM (HEM) and poor metabolizers (PM), respectively. A 58% protein binding (PB) of voriconazole in human plasma was employed to caculate the percentage of free drug (f, f = 1-PB) (Mouton et al. 2005)

The wild-type MIC for six *Aspergillus spp.* distribution data were obtained from a study published by Espinel-Ingroff et al. (2010). The voriconazole MICs for these pathogens varied between 0.03 and 2.0 mg/L (Table 1).

2.2. Monte Carlo simulation

A pharmacodynamic study of a murine candidiasis model showed that the best predictor of response to voriconazole therapy was the free area under the plasma concentration–time curve (AUC) from 0 to 24 h ($fAUC_{24}$) divided by the MIC ($fAUC_{24}$/MIC) ≥ 25 (Andes et al. 2003; Theuretzbacher et al. 2006). The MCS were performed for the standard dosage regimen in order to predict the outcomes of the standard dosage regimen in patients.

The results of the MCS were expressed as the probability of target attainment (PTA) and and cumulative fraction of response (CFR) of $fAUC_{24}$/MIC ≥ 25. A CFR result of $\geq 90\%$ represented the standard dosage regimen against a population of organisms effectively, as previously established by the OPTAMA program (Masterton et al.2005).

2.3. PTA analysis results

The chosen target was fAUC24/MIC ≥ 25 for three CYP2C19 genotypes. The Figure 1 shows the probability of PK/PD target attainment by MICs for the three genotypes under the standard dosing regimen. On the basis of simulation results, for EM, the use of voriconazole 200 mg every 12 h provided PTA values which were higher than 90% when MICs ≤ 0.25 mg/L; for HEM and PM, all simulated patients reached the target until MICs > 0.5 mg/L and MICs > 1 mg/L respectively.

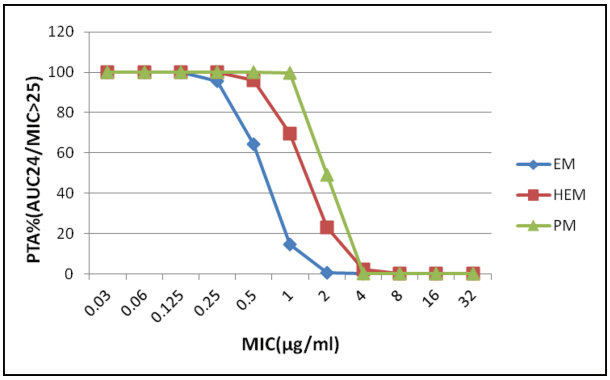

Fig. 1: Probability of target attainment as a function of the MIC for 5,000 simulated subjects given voriconazole.

Table 2: Expected cumulative fraction of response (CFR) for voriconazole. The chosen target was $fAUC_{24}$/MIC $\geq$25 for three genotypes

Species	CFR (%)		
	EM	HEM	PM
A. fumigatus	57.22	93.77	98.20
A. flavus	72.54	88.99	98.99
A. terreus	60.22	90.17	98.87
A. niger	47.01	80.57	94.18
A. nidulans	79.47	90.73	96.14
A. versicolor	59.36	77.41	87.88

2.4. Cumulative fraction of response analysis

Table 2 shows the assessment of CFR for standard voriconazole dosage regimen evaluated based on the $fAUC_{24}$/MIC $\geq$25 in the treatment of six *Aspergillus.* infections for three genotypes. For EM, the values of CFR for the six *Aspergillus spp.* with 200 mg every 12 h were all lower than 90%. Whilst for HEM, the values of CFR for *A. fumigatus* (93.77%), *A. terreus* (90.17%) and *A. nidulans*(90.73%) were higher than 90%; the CFRs of *A. flavus, A. niger, and A. versicolor* were noted to be lower (88.99%, 80.57%, and 77.41%, respectively) than 90%. For PM, the CFR value of *A. versicolor* (87.88%) was only fractionally lower than 90%; among the remaining fungus, CFR values of $\geq 90\%$ were obtained with the using of the standard dose regimen in PM. The standard dosage regimen was poorly active against *A. versicolor* in three genotypes (CFRs varied from 59.36% to 87.88%).

3. Discussion

For the first time, we evaluated the standard voriconazole dosage regimen by linking *Aspergillus* MIC data with the pharmacokinetic profile of different CYP2C19 genotypes through MCS method. Voriconazole is commonly used for treatment of invasive infections caused by *Aspergillus spp.* However, reports of *Aspergillus'* azole resistance are emerging, and resistance is now recognised as a cause of treatment failure (Vermeulen et al. 2012). Therefore, the efficacy of the current voriconazole dosage regimen should be re-evaluated in the light of emerging of *Aspergillus* resistance.

Besides the sensitivity of *Aspergillus* to voriconazole, CYP2C19 polymorphism is a major factor of efficacy in patients (Hamada et al. 2012; Weiss et al. 2009; Berge et al. 2011). In order to attain therapeutic concentrations, therapeutic drug monitoring (TDM) of voriconazole is usually conducted to adjust clinical doses (Park et al. 2012). However, adverse reactions may have already happened in PM or best treatment may fail to be attained in EM before the data of high or low serum concentration will be provided (Suan et al. 2011). Hence, it is necessary to adjust regimens according patient's genotype before drug administration, especially for Asian populations in which the percentage of PM is approximately 7 times higher than in Caucasians (Desta et al. 2002). Currently, there is only one standard dosage regimen (400 mg twice on the first day and 200 mg twice on the following days orally) for all CYP2C19 genotypes. In this study, we firstly evaluated the standard voriconazole dosage regimen by linking *Aspergillus* MIC data with the pharmacokinetic profile of different CYP2C19 genotypes through the MCS method.

MCS, a technical statistical method, was invented in 1949 to predict the probability or likelihood of certain consequences. The method was widely used in various fields, such as society, economy, industry, commerce and medicine (Koomanachai et al. 2009). MCS provideds a computer-based mathematical construct that can simultaneously integrate different variables such as tissue concentrations of an antibiotic and antimicrobial susceptibility each with its own probability distribution together with information about the PK-PD measure associated with efficacy, to estimate the likelihood of achieving the PK-PD target (and thus, the likelihood of achieving cure) (Bradley et al. 2010). On the basis of simulation results, the standard dosage regimen for poor metabolizers (PM) with *Aspergillus* infections was effective except for *A.versicolo* ; for heterozygous extensive metabolizers (HEM), *A. fumigatus*, *A.terreus* and *A.nidulans* infections could be treated effectively with the standard dosage regimen; for extensive metabolizers (EM), the standard voriconazole dosage regimen failed to achieve the best outcome *in vivo* for the six *Aspergillus spp*. Increased doses (e.g. 300 mg bid) or even changing the antifungal drug was needed for EM and most HEM patients with *Aspergillus* infection. This is consistent with a previous conclusion that a maintenance dose of 200 mg every 12 h may probably not be adequate for the effective treatment or prophylaxis of severe fungal infections (Geist et al. 2013). High variability in voriconazole exposure, as well as low steady-state trough plasma concentrations would lead to disease progression. On the contrary, another Monte Carlo stimulation (Wang et al.2014) in patients with invasive fungal infections (IFIs) concluded that *Aspergillus* infections could be treated effectively with 200 mg of voriconazole administered intravenously or orally twice daily. In that study, the PK data was collected from IFIs patients who used omeprazole, dexamethasone or azithromycin as concomitant medication which may influence the PK of voriconazole. Secondly, the PK parameters had not been separated according to CYP2C19 genotype of IFIs patients. Thirdly, MIC distributions for the *Aspergillus* were different from our study. For the above three reasons, different PK parameters for voriconazole and MIC distributions were used in the simulation, which led to different results.

This study suggests that pharmacogenomic variations can impact drug response and providing the same dosing regimen for all genotypes can lead to treatment failures. In current clinical practice, dose adjustments to voriconazole therapy are simply based on body weight in the first administration (Matsumoto et al.2009). However, a case report suggested if an obese patient who was dosed on total body weight is also a CYP2C19 poor metabolizer, the serum voriconazole concentrations will be further elevated, potentially leading to drug-induced toxicity (Moriyama et al. 2013). Although the distribution of voriconazole in adipose tissue of animals and humans is unknown, another recent report suggested that voriconazole might not distribute extensively into fat tissue in humans (Pai and Lodise 2011).

Recently, CYP2C19*17, a new CYP2C19 genotype, was detected and it was needed to be concerned about. The allele is quite common in Europeans and Africans, but rare in Asians. Carriers with at least one*17 allele were originally referred as ultrarapid metabolizers (UMs), which would result in significantly lower AUC and C_{max} and higher CL/F values of voricoanzole than what was found for homozygous EMs and PMs (Wang et al. 2009). This suggested that poor treatment outcome was probably observed in UMs using 200 mg bid oral. Increasing doses, increasing frequency of administration or even changing the antifungal drug was needed for UMs (Malingré et al. 2012).

There are two limitations to the present study. (i) PK of voriconazole collected were conducted in a small population of healthy volunteers, which was not accurate enough for estimating the exposure of patients who may be immunocompromised and/or infected with *Aspergillus*. (ii) Simulation of other dosage regimens (like 300 mg bid) were not conducted for lacking of PK parameters from different CYP2C19 genotypes. In the clinic, while the dosage (200 mg bid) is FDA approved, much larger doses are used when necessary, in order to optimize plasma concentrations.

In conclusion, using MCSs, the standard dosage regimen (200 mg bid orally) for PM with *Aspergillcs* infections was effective except for *A.versicolor*, and increasing dose (e.g. 300 mg bid) or even changing the antifungal drug was needed for EM and most HEM patients with *Aspergillus* infection. Instead of using a standard dosage regimen for all patients, the voriconazole dosage regimen needs to be optimized for patients with different CYP2C19 genotypes.

Further work needs to focus on the optimization of voriconazole dose regimens for the treatment of different infections with invasive fungi. Rational drug use is important to prevent an escalation in antifungual resistance and to maximize the likelihood of a favorable clinical response, as well as to minimize the probability of exposure-related toxicity.

4. Experimental

4.1. Acquisition of PK parameters and microbiological information

The PK parameters of voriconazole in different CYP2C19 genotypes were obtained from a published study (Lee et al. 2012). In this study, healthy volunteers were classified into three groups by CYP2C19 phenotype: EM (CYP2C19*1/*1, n = 6), HEM(CYP2C19*1/*2, *1/*3, n = 6) and PM(CYP2C19*2/*2, *2/*3, *3/*3, n = 6). Individual PK parameters were calculated by noncompartmental method using WinNonlin 5.2.1. The CLss/F was significantly different among the three CYP2C19 genotypes (P = 0.006).

The wild-type MIC for six *Aspergillus spp.* distribution data were obtained from the study published by Espinel-Ingroff et al. (2010). In the study, the wild-type MIC distributions of voriconazole for six *Aspergillus spp.* were defined using aggregated MIC data gathered from five laboratories in Europe and the United States.

4.2. MCS

The MCS accounted for the variability in the population pharmacokinetic parameters (PPK) of different CYP2C19 phenotype as well as the MIC data, to determine the PTA value of $fAUC_{24}/MIC \geq 25$. The estimated mean values and the interindividual variances of the population parameters (CL and F) from the published study, which were assumed to follow lognormal distribution, were analyzed by MCS. The AUC_{24} was then calculated with the following formula (Fernandez de Gatta Mdel et al. 2009):

$AUC_{24} = Dose_{24} \times F/CL$

In this equation, $Dose_{24}$ stands for the daily dose, CL for the clearance and F for oral bioavailability. For multiple dose regimens, CL stands for clearance at steady state.

Discrete MIC distributions of the *Aspergillus* were based on the MIC frequencies (Table 1). The range of possible values was restricted to the 95% CI for discarding marginal variable values in the random process. A MCS with 5000 patients was performed using Crystal Ball (Ver7.2.2) software (Decisioneering Corporation, http://crystalball.com)

The PTA (defined as the probability that at least a specific value of a PK/PD index is achieved at a certain MIC) and CFR (defined as the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms) were estimated by the MCS (Mouton et al. 2005; Canut et al. 2012). The corresponding PTA was calculated with one fixed MIC value ranging from 0.03 to 32 mg/L, and the calculation of the CFR used the data from the MIC distribution. The dosage regimen was evaluated by comparing the value of PTA and CFR in these simulated patients.

Conflict of interests: The authors declare that no competing interests exist.

References

Andes D, Marchillo K, Stamstad T, Conklin R (2003) *In vivo* pharmacokinetics and pharmacodynamics of a new triazole, voriconazole, in a murine candidiasis model. Antimicrob Agents Chemother 47: 3165–3169.

Berge M, Guillemain R, Trégouet DA, Amrein C, Boussaud V, Chevalier P, Lillo-Lelouet A, Le Beller C, Laurent-Puig P, Beaune PH, Billaud EM, Loriot MA (2011) Effect of cytochrome P4502C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol 67: 253–260.

Bradley JS, Garonzik SM, Forrest A, Bhavnani SM (2010) Pharmacokinetics, pharmacodynamics, and Monte Carlo simulation: selecting the best antimicrobial dose to treat an infection. Pediatr Infect Dis J 29: 1043–1046.

Brown GD, Denning DW, Gow NAR, LevitzS, Netea M, White T (2012) Human fungal infections: the hidden killers. Sci Transl Med 4: 165rv13.

Canut A, Isla A, Betriu C, Gascoń A (2012) Pharmacokinetic–pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four Western European countries. Eur J Clin Microbiol 31: 2227–2235.

Desta Z, Zhao X, Shin JG, Flockhart DA (2002) Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 41: 913–958.

Espinel-Ingroff A, Diekema DJ, Fothergill A, Jonhson E, Pelaez T, Pfaller MA, Rinaldi MG, Canton E, Turnidge J (2010) Wild-type MIC distributions and epidemiological cutoff values for the triazoles and six Aspergillus spp. for the CLSI broth microdilution method (M38-A2 Document).J Cli Microbiol 48: 3251–3257.

Fernandez de Gatta Mdel M, Santos Buelga D, Sanchez Navarro A, Dominguez-Gil A, García MJ (2009) Vancomycin dosage optimization in patients with malignant haematological disease by pharmacokinetic/pharmacodynamic analysis. Clin Pharmacokinet 48: 273–280.

Geist MJ, Egerer G, Burhenne J, Riedel KD, Weiss J, Mikus G. (2013) Steady-state pharmacokinetics and metabolism of voriconazole in patients. J Antimicrob Chemother 68: 2592–2599.

Goldstein JA (2001) Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. Br J Clin Pharmacol 52:349–355.

Hamada Y, Seto Y, Yago K, Kuroyama M (2012) Investigation and threshold of optimum blood concentration of voriconazole: adescriptive statistical meta-analysis. J Infect Chemother 18: 501–507.

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347: 408–415.

Herbrecht R (2004) Voriconazole: therapeutic review of a new azole antifungal. Expert Rev Anti Infect Ther 2: 485–497.

Howard SJ, Arendrup MC (2011) Acquired antifungal drug resistance in Aspergillus fumigatus: epidemiology and detection. Med Mycol 49 (Auppl 1): S90 –95.

Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M (2004) Pharmacokinetics of voriconazoleand cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 75: 587–588.

Koomanachai P, Crandon JL, Kuti JL, Nicolau DP (2009) Comparative pharmacodynamics for intravenous antibiotics against Gram-negative bacteria in Europe between 2002 and 2006: a report from the OPTAMA program. Int J Antimicrob Agents 33: 348–353.

Kuti JL, Nicolau DP (2005) Making the most of surveillance studies: summary of the OPTAMA Program. Diagn Microbiol Infect Dis 53: 281–287.

Lee SH, Kim BH, Nam WS, Yoon SH, Cho JY, Shin SG, Jang IJ, Yu KS (2012) Effect of CYP2C19 Polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers. J Clin Pharmacol 52: 195–203.

Malingré MM, Godschalk PC, Klein SK (2012) A case report of voriconazole therapy failure in a homozygous ultrarapid CYP2C19*17/*17 patient comedicated with carbamazepine. Br J Clin Pharmacol 74: 205–206.

Matsumoto K, Ikawa K, Abematsu K, Fukunaga N, Nishida K, Fukamizu T, Shimodozono Y, Morikawa N, Takeda Y, Yamada K (2009) Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. Int J Antimicrob Agents 34: 91–94.

Masterton RG, Kuti JL, Turner PJ, Nicolau DP (2005) The OPTAMA programme: utilizing MYSTIC (2002) to predict critical pharmacodynamic target attainment against nosocomial pathogens in Europe. J Antimicrob Chemother 55: 71–77.

Mikus G, Schöwel V, Drzewinska M, Rengelshausen J, Ding R, Riedel KD, Burhenne J, Weiss J, Thomsen T, Haefeli WE (2006) Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 80: 126–135.

Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL (2005) Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 55: 601–607.

Moriyama B, Jarosinski PF, Figg WD, Henning SA, Danner RL, Penzak SR, Wayne AS, Walsh TJ (2013) Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype. Pharmacotherapy 33: e19–e22.

Pai MP, Lodise TP (2011) Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother 55: 2601–2605.

Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, Song KH, Choe PG, Kim NJ, Jang IJ, Oh MD, Yu KS (2012) The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 55: 1080–1087.

Rengelshausen J, Banfield M, Riedel KD, Burhenne J, Weiss J, Thomsen T, Walter-Sack I, Haefeli WE, Mikus G (2005) Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 78: 25–33.

Suan D, O'Connor K, Booth DR, Liddle C, Stewart GJ (2011) Voriconazole toxicity related to polymorphisms in CYP2C19. Intern Med J 41: 364–365.

Sun HK, Kuti JL, Nicolau DP (2005) Pharmacodynamics of antimicrobials for the empirical treatment of nosocomial pneumonia: a report from the OPTAMA Program. Crit Care Med 33: 2222 –2227.

Theuretzbacher U, Ihle F, Derendorf H (2006) Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet 45: 649–663.

Vermeulen E, Cooreman S, Maertens J, Jeurissen A, Lagrou K (2012) Azole resistance in Aspergillus: an emerging problem? Acta Clin Belg 67: 322–327.

Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L, Chen Y, Hu DL, Wang D, Zhou HH (2009) The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 65: 281–285.

Wang T, Chen S, Sun J, Cai J, Cheng X, Dong H, Wang X, Xing J, Dong W, Yao H, Dong Y (2014) Identification of factors influencing the pharmacokinetics of voriconazole and the optimization of dosage regimens based on Monte Carlo simulation in patients with invasive fungal infections. J Antimicrob Chemother 69: 463–470.

Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J, Haefeli WE, Mikus G (2009) CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol 49: 196–204.