World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i14.1828

World J Hepatol 2015 July 18; 7(14): 1828-1833
ISSN 1948-5182 (online)

EDITORIAL

Voriconazole and the liver

Romeo-Gabriel Mihăilă

Romeo-Gabriel Mihăilă, Faculty of Medicine, Lucian Blaga University of Sibiu, 550169 Sibiu, Romania

Author contributions: Mihăilă RG solely contributed to this manuscript.

Conflict-of-interest statement: The author has no conflict-of-interest related to this article.

Correspondence to: Romeo-Gabriel Mihăilă, MD, PhD, Faculty of Medicine, Lucian Blaga University of Sibiu, Str Lucian Blaga, 2A, 550169 Sibiu,
Romania. romeomihaila@yahoo.com
Telephone: +40-269-215050
Fax: +40-269-218365

Received: January 21, 2015
Peer-review started: January 21, 2015
First decision: February 7, 2015
Revised: February 21, 2015
Accepted: April 10, 2015
Article in press: April 14, 2015
Published online: July 18, 2015

Abstract

Voriconazole is an azole useful for the prophylaxis and the treatment of aspergillosis and other fungal infections in immunosuppressed subjects, as those found in aplasia after aggressive polychemotherapy treatments, after hematopoietic stem cell, liver or lung transplantation. Its administration in therapeutic doses lead to extremely varied serum levels from patient to patient and even to the same patient. The explanations are varied: nonlinear pharmacokinetics, certain patient-related factors, including genetic polymorphisms in the cytochrome *P450 2C19* gene, the kidney and liver function, simultaneous administration with other drugs metabolised by the same cytochrome. It is recommended to maintain the serum concentrations of voriconazole between 1.5 and 4 μg/mL. At lower values its efficacy decreases and at higher values the risk of neurological toxicity increases. Even at these concentrations it is not excluded the possible appearance of a variety of toxic effects, including on the liver, manifested by cholestasis, hepatocytolisis, or their combination. It is recommended to monitor the clinical and laboratory evolution of all patients treated with voriconazole, and of the serum levels of the drug of those who belong to risk groups, even if there is still no consensus on this issue, given the lack of correlation between the serum level and the occurrence of adverse effects in many patients.

Key words: *CYP2C19*; Pharmacokinetics; Liver toxicity; Therapeutic drug monitoring; Voriconazole

Core tip: Voriconazole is an azole useful for the prophylaxis and the treatment of aspergillosis and other fungal infections in immunosuppressed subjects. Its administration in therapeutic doses lead to extremely varied serum levels from patient to patient and even to the same patient. It is recommended to maintain the serum concentrations of voriconazole between 1.5 and 4 μg/mL. At lower values its efficacy decreases and at higher values the risk of neurological toxicity increases. Even at these concentrations it is not excluded the possible appearance of a variety of toxic effects, including on the liver, manifested by cholestasis, hepatocytolisis, or their combination.

Mihăilă RG. Voriconazole and the liver. *World J Hepatol* 2015; 7(14): 1828-1833 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i14/1828.htm DOI: http://dx.doi.

org/10.4254/wjh.v7.i14.1828

INTRODUCTION

This article is written for clinicians who use voriconazole. Starting from pharmacological data, the aim of this literature synthesis is to find explanations and to establish correlations with clinical manifestations that may occur during its use.

Voriconazole is a usual antifungal drug with a good bioavailability, which is bound to plasma protein in a high percentage[1]. It is considered to be the drug of choice for the treatment of invasive aspergillosis[2]. Voriconazole was approved by the United States Food and Drug Administration in 2002[3]. Its metabolisation takes place in the liver, at the level of P450 CYP2C19[1,2], CYP2C9, and CYP3A4, and its products of metabolism are excreted by the kidneys[2]. Only 2% of the dose excreted in urine is unchanged. There is a variety of drug-drug interactions that must be considered. The ratio between the area under the time-concentration profile and the minimal inhibitory concentration is the main pharmacokinetic/pharmacodynamic parameter for voriconazole[2]. It is active against a large variety of fungi, but it also can have adverse effects, including the liver toxicity[1]. This aspect deserves to be good understood, as it is commonly administered to patients with various associated diseases, and sometime immunocompromised, together with other drugs, for serious infections.

LIVER TOXICITY

Liver toxicity can sometimes be present. From a total of 68115 regarded liver injuries, 2.9% of them (1964 cases, including 112 with acute liver failure) were related to antimycotics, during a period of 8 years, as was found in FAERS database. All antimycotics with systemic action or absorption can induce such toxicity, including voriconazole[4]. This was shown in 2 of 21 patients with chronic pulmonary aspergillosis treated with oral voriconazole, which imposed the drug discontinuation, in a recent published study[5]. In a prospective study, which included 95 patients, 6.3% of them developed liver toxicity under voriconazole[6]. In a prospective, open-label, multicenter study in which voriconazole was given to 48 patients, as first-line treatment for chronic pulmonary aspergillosis, 16.9% of treated patients had abnormal liver function tests. Liver serious adverse events were noted at 2.8% of them and imposed to stop the drug administration. The authors did not show any association between voriconazole serum levels and the appearance of adverse effects[7]. In a retrospective study made on a group of 105 patients who received a lung transplant and were treated with voriconazole, it was found that 51% of them developed liver toxicity and 34% of them had to discontinue the treatment for this reason. The univariate statistical analysis established that the following factors were associated with liver toxicity: age younger as 40 years, azathioprine treatment, presence of cystic fibrosis, history of hepatic disease and early start of voriconazole. The authors have developed an algorithm predictive model to predict liver toxicity, that has an accuracy of 70%, using the above risk factors. The start of voriconazole in the first 30 d since the date of transplantation was the sole factor independently associated with liver toxicity in the multivariable logistic regression analysis[8]. Patients aged $\geqslant$ 60 years were significantly more likely to have higher initial voriconazole plasma levels, while those with cystic fibrosis - higher ones, in a prospective study on 93 lung transplant recipients who received prophylaxis with voriconazole. Voriconazole serum levels were not correlated with the presence or absence of liver toxicity, neither here[9].

A worsening of liver function tests was shown at 69% of patients with severe liver dysfunction who received at least 4 doses of voriconazole, in an observational study. Most of them had a combination of liver cytolysis and cholestasis (45%). An increase of transaminases was shown in 35%, and an isolated cholestasis was present in 15% of them. All of them had a severe reaction. There was noted a correlation between the initial dose of more than 300 mg (4.5 mg/kg) and the risk of liver toxicity. These patients represent a special category that needs a frequent monitoring of liver function tests[10].

Two percent of patients with liver transplantation who received different antifungal drugs as targeted prophylaxis (including voriconazole in 54% of 145 subjects) or universal voriconazole prophylaxis (237 patients) developed toxicity which required drug discontinuation, after a median treatment of 11, and, respectively, 6 d[11]. It was shown that liver dysfunction had greater rates under voriconazole, as fluconazole or itraconazole, but voriconazole decreased transplant mortality in a meta-analysis which included 5122 patients who received antifungal prophylaxis[12].

Prophylaxis with voriconazole was better tolerated by patients who received allogeneic hematopoietic stem-cell transplant as those with itraconazole. It was shown that 12.9% of those who received voriconazole had liver toxicity/dysfunction, which was the most frequent adverse effect[13].

A recently published method uses unlabeled or deuterated methanol, followed by GC-MS analysis in order to speed up the metabolic profiling of fatty acids, useful for establishing the presence and the mechanism of voriconazole induced liver toxicity, and the possibility to use fatty acids as markers of toxicity[14]. Frechen *et al*[15] developed a coupled dynamic model useful to study the interaction of voriconazole (a CYP3A inhibitor) and midazolam (a CYP3A substrate). Thus, it is possible to maximize the information obtained from clinical drug-drug interactions studies[15].

Therefore, among the liver side effects of voriconazole, jaundice, including the cholestatic one, is more common while hepatomegaly or hepatitis occurs

less frequently. It rarely induces liver failure and very rarely hepatic coma. So the liver damage produced by voriconazole is mainly due to cholestasis, and more rarely can be cytotoxic or mixed.

Voriconazole is not involved in the appearance of autoimmune hepatitis, but an increase in the levels of immunosuppressive drugs (cyclosporine or tacrolimus) used in patients after solid organ transplants or with autoimmune disorders was reported during coadministration with this antifungal drug. One of five such patients developed a moderate increase in hepatic enzymes. This combination of drugs requires immunosuppressive dose adjustment (by its reducing)[16].

IS THERAPEUTIC DRUG MONITORING NECESSARY?

Serum levels

Voriconazole serum levels are important in relation to efficacy and toxicity: a lack of clinical response has been seen at below 1 or 2 μg/mL and toxic effects appear frequently at above 5 μg/mL[1]. But, it was shown that voriconazole steady-state concentrations had a large variability from patient to patient, with values between 0 and 16.6 μg/mL, in a study that included 69 patients with primarily acute leukemia under intensive chemotherapy. In this study, about 20% of patients had concentrations < 1 μg/mL[17], therefore, ineffective. This variability was even larger (< 0.10-20 mg/L) in a study made on 108 patients of whom 77.8% had a hematologic cancer, who were treated for a presumed fungal infection[18].

There may be several explanations for this inter-patient variability: the nonlinear pharmacokinetics and some patient-related data, as gender, age, weight, a possible liver disease, and genetic polymorphisms in the cytochrome *P450 2C19* gene (*CYP2C19*), so that the knowledge of *CYP2C19* genotype can be used to establish initial voriconazole dose and the modality of therapeutic drug monitoring, in order to obtain the therapeutic effects without toxicity[3]. But, contrary to theoretical considerations, it was observed that *CYP2C19* and *CYP2C9* genotypes had only a minor influence on the serum levels of voriconazole, though the 4 patients who were homozygous for the *2C19*2* genotype had higher average serum levels of the drug, in a prospective study which included 95 patients. It is notable that patients who had hallucinations had higher average voriconazole levels[6], which highlights the importance of careful clinical monitoring of patients. But in the study of Chu *et al*[18], mentioned above, where was no relationship between therapeutic drug levels of voriconazole and the response to this antifungal treatment, and unlike other studies, there was no association with an increase of hepatotoxicity at voriconazole levels > 5.5 mg/L. This observation suggests that therapeutic drug monitoring could be limited to a subset of high-risk patients[18]. In another multicenter study which included 264 patients with hematological diseases, who received voriconazole for prophylaxis or treatment of invasive aspergillosis, a large range of plasma concentration (between < 0.20 and 13.47 μg/mL) was also seen. The authors found only an association between voriconazole plasma troughs and the use of omeprazole. They did not find any correlation with other parameters, as age, gender, dose or route of voriconazole administration (including those by nasogastric tube), *CYP2C19*2* genotype, possible abnormalities of gastrointestinal tract, serum levels of liver enzymes or creatinine, with treatment outcome of patients with invasive aspergillosis, or with the cases of reported toxicity to this drug. This study also raises the question of the utility of routine clinical monitoring of voriconazole plasma concentrations[19].

It was shown that 40 immunocompromised children had higher average exposure to voriconazole at steady state during oral treatment with 200 mg q12h than adults, so that a weight-based oral dose could be more appropriate for them[20].

Given the accumulated clinical and laboratory experience, in order to obtain therapeutic efficacy and to avoid toxicity, most authors suggest a serum voriconazole concentrations between 1.5 and 4 μg/mL[9,21]. The lower limit was set considering the significantly higher success rate of fungal infections treatment over this level, and the superior limit - due to the fact that above its it was shown that adverse neurological effects appeared significantly more frequent. The metaanalysis included 12 studies and also found an increase of liver adverse effects at higher blood concentrations, but obtained data did not allow the formulation of a limit above which the risk increases significantly[19,21].

Arguments for clinical monitoring

The following categories of patients should be carefully monitored, although there is no consensus in this respect: the children, the patients with cystic fibrosis, liver or renal failure (including those under chronic hemodialysis), and those who are concomitant under treatment with other drugs, which voriconazole could interfere with[1]. There was found no relationship between plasma voriconazole concentrations and age, gender, genotype or concomitant administration of proton pump inhibitors, but there was a correlation between the drug concentration and higher serum levels of serum alkaline phosphatase, aspartate aminotransferase, and bilirubin, in the study published by Saini *et al*[17].

A case of triple drug combination was published in the literature: lansoprazole, voriconazole (400 mg/d) and tactolimus. It was found that the concentration of voriconazole became half of the initial one (from 5.0 ng/mL) and those of tactolimus also fell after reducing the dose of lansoprazole [from 60 mg/d intravenous (*iv*) to 15 mg/d per os] in a patient with *CYP2C19* and *CYP3A5* heterozygous mutations. This is an example of drug interaction: the lowering of lansoprazole dose decreased voriconazole concentration and this seems

to be the explanation for the decrease of those of tacrolimus[22]. This drug monitorization needs future controlled studies for its validation and for a personalized treatment, with dose adjusted according to the patient[1].

Another explanation for high voriconazole levels consists in the presence of inflammation, due to the fact that inflammatory stimuli can modify the activities and expression levels of cytochrome P450 isoenzymes. Indeed, in a retrospective chart review which included 128 patients found under voriconazole treatment, higher drug trough concentrations were present in those with severe inflammation (C-reactive protein about 6.2 mg/L), although the dose of the drug was similar reported on mg/kg body weight. Every increase of C-reactive protein with 1-mg/L contributed to an elevation of voriconazole trough concentration with 0.015 mg/L[23]. It was found that lipopolysaccharide did not exacerbate the effect of voriconazole, which induces non-idiosyncratic liver injury, unlike clozapine and ketoconazole[24].

An association between the use of voriconazole and a higher survival probability in liver transplant recipients with invasive aspergillosis was found, comparing to other antifungal drugs[25]. In another retrospective study, 39 patients with acute-on-chronic liver failure developed invasive pulmonary aspergillosis; it was shown that those treated with voriconazole had better prognosis comparing with those without antifungal drug. Although the dose of voriconazole was not adjusted, there was no negative impact on renal or hepatic function, but this does not preclude the need for careful monitoring the function of vital organs for the metabolism of voriconazole[26]. Multiple logistic regression analysis made on 39 patients established that persistent high trough concentration of this drug may increase the risk of liver toxicity; this fact may be avoided by reducing the trough concentration to < 4 μg/mL[27].

An important drug association that may be found in oncohematology is between voriconazole and tacrolimus, especially in patients who received allogeneic bone marrow transplantation. Voriconazole at clinically relevant concentrations will increase more than two-fold the serum levels of tacrolimus, by the inhibition of its hepatic metabolism[28].

Baseline liver impairment of patients with renal dysfunction was found to be a significant predictor of worsening renal function in multivariate analyses in the seventh day of voriconazole treatment[29].

HOW TO REDUCE THE TOXICITY OF VORICONAZOLE?

It would be ideal to have the possibility to measure serum concentrations of voriconazole in all patients and to ensure that during treatment they are between the recommended limits, although we know that it is not a way able to prevent the possible occurrence of adverse effects in all cases.

But lowering the dose is another way to reduce the likelihood of adverse effects induced by voriconazole administration, especially when we are not able to monitor the serum drug level. That was done in a study that included 83 patients who were subjected to allogeneic hematopoietic stem cell transplantation, and who received *iv* voriconazole (only 100 mg two times per day) since the time of conditioning regimen until their neutrophils exceeded 0.5×10^9/L. This led to a rate of invasive fungal infections of only 8.43%, compared to 18.06% in the group treated with oral fluconazole (200 mg/d). This difference was statistically significant, and, very important, the frequency of functional liver abnormalities was similar under the two drugs[30]. The question which remains is whether the fungal infection rate would have not been lower under a normal dose of voriconazole, and also whether the benefit gained by lowering the rate of fungal infections would not have been canceled by the increased toxicity induced by voriconazole.

Other ways to prevent the potential drug toxicity, including those on the liver, are avoiding the use of this drug in patients with severe liver disease or advanced renal failure, and clinical (for the detection of the first events that might suggest toxicity, *e.g.*, hallucinations) and laboratory monitoring (transaminases, bilirubin, cholestatic enzymes, serum creatinine), especially in patients who are in treatment with other drugs that are metabolized by cytochrome P450. Voriconazole is recommended for patients with liver disease only if the benefit outweighs the potential risk.

Another way to reduce the adverse effects (including those on the liver) induced by azols consists in the development of new antifungal agents that are more selective for the target fungal enzyme CYP51, in comparison with the human CYP enzymes CYP3A4. These newly created agents have less avid metal-binding groups and molecular changes in order to enhance their potency. Such an oral agent is 7 d (VT-1161), found in phase 2 of clinical trials[31].

CONCLUSION

Voriconazole serum levels are not correlated with the presence or absence of liver toxicity in many studies, but in others an increase of liver adverse effects at higher blood concentrations was shown, although obtained data did not allow the formulation of a limit above which the risk increases significantly.

Patients who have hallucinations have, probably, higher average voriconazole levels.

Most authors suggest a steady-state serum voriconazole concentrations between 1.5 and 4 μg/mL.

A correlation between the drug concentration and higher serum levels of serum alkaline phosphatase, aspartate aminotransferase, and bilirubin was found.

Therapeutic drug monitoring could be limited to a subset of high-risk patients, as those with severe liver dysfunction, who are prone to develop liver toxicity under voriconazole, especially if the initial dose is more than 300 mg (4.5 mg/kg). The following categories of

high-risk patients should also be carefully monitored, although there is no consensus in this respect: the children, the patients with cystic fibrosis, liver or renal failure (including those under chronic hemodialysis), and those who have severe inflammation or are concomitant under treatment with other drugs, which voriconazole could interfere with.

A weight-based oral dose could be more appropriate for children.

In order to reduce the likelihood of its adverse effects, lowering the *iv* dose of voriconazole was able to reduce the fungal infection rate comparing with oral fluconazole, but there is no study to prove that its efficiency is the same with that of normal dose.

A way to avoid its potential toxicity is the development of new antifungal agents that are more selective for the target fungal enzyme CYP51, in comparison with the human CYP enzymes CYP3A4.

REFERENCES

1 **Hulin A**, Dailly E, Le Guellec C. [Level of evidence for therapeutic drug monitoring of voriconazole]. *Therapie* 2011; **66**: 109-114 [PMID: 21635857]

2 **Bellmann R**. Pharmacodynamics and pharmacokinetics of antifungals for treatment of invasive aspergillosis. *Curr Pharm Des* 2013; **19**: 3629-3647 [PMID: 23278532]

3 **Owusu Obeng A**, 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**: 703-718 [PMID: 24510446 DOI: 10.1002/phar.1400]

4 **Raschi E**, Poluzzi E, Koci A, Caraceni P, Ponti FD. Assessing liver injury associated with antimycotics: Concise literature review and clues from data mining of the FAERS database. *World J Hepatol* 2014; **6**: 601-612 [PMID: 25232453 DOI: 10.4254/wjh.v6.i8.601]

5 **Cucchetto G**, Cazzadori A, Conti M, Cascio GL, Braggio P, Concia E. Treatment of chronic pulmonary aspergillosis with voriconazole: review of a case series. *Infection* 2015; **43**: 277-286 [PMID: 25432571]

6 **Zonios D**, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, Skinner J, Bennett JE. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis* 2014; **209**: 1941-1948 [PMID: 24403552 DOI: 10.1093/infdis/jiu017]

7 **Saito T**, Fujiuchi S, Tao Y, Sasaki Y, Ogawa K, Suzuki K, Tada A, Kuba M, Kato T, Kawabata M, Kurashima A, Sakatani M. Efficacy and safety of voriconazole in the treatment of chronic pulmonary aspergillosis: experience in Japan. *Infection* 2012; **40**: 661-667 [PMID: 22956473 DOI: 10.1007/s15010-012-0322-x]

8 **Luong ML**, Hosseini-Moghaddam SM, Singer LG, Chaparro C, Azad S, Lazar N, Boutros PC, Keshavjee S, Rotstein C, Husain S. Risk factors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. *Am J Transplant* 2012; **12**: 1929-1935 [PMID: 22486950 DOI: 10.1111/j.1600-6143.2012.04042.x]

9 **Mitsani D**, Nguyen MH, Shields RK, Toyoda Y, Kwak EJ, Silveira FP, Pilewski JM, Crespo MM, Bermudez C, Bhama JK, Clancy CJ. 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**: 2371-2377 [PMID: 22330924 DOI: 10.1128/AAC.05219-11]

10 **Solís-Muñoz P**, López JC, Bernal W, Willars C, Verma A, Heneghan MA, Wendon J, Auzinger G. Voriconazole hepatotoxicity in severe liver dysfunction. *J Infect* 2013; **66**: 80-86 [PMID: 23041040 DOI: 10.1016/j.jinf.2012.09.011]

11 **Eschenauer GA**, Kwak EJ, Humar A, Potoski BA, Clarke LG, Shields RK, Abdel-Massih R, Silveira FP, Vergidis P, Clancy CJ, Nguyen MH. Targeted versus universal antifungal prophylaxis among liver transplant recipients. *Am J Transplant* 2015; **15**: 180-189 [PMID: 25359455 DOI: 10.1111/ajt.12993]

12 **Xu SX**, Shen JL, Tang XF, Feng B. Newer antifungal agents for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis. *Transplant Proc* 2013; **45**: 407-414 [PMID: 23375330 DOI: 10.1016/j.transproceed.2012.07.149]

13 **Marks DI**, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, Miller PJ, Ribaud P, Schlamm HT, Solano C, Cook G. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol* 2011; **155**: 318-327 [PMID: 21880032 DOI: 10.1111/j.1365-2141.2011.08838.x]

14 **Chen GY**, Chiu HH, Lin SW, Tseng YJ, Tsai SJ, Kuo CH. Development and application of a comparative fatty acid analysis method to investigate voriconazole-induced hepatotoxicity. *Clin Chim Acta* 2015; **438**: 126-134 [PMID: 25150729 DOI: 10.1016/j.cca.2014.08.013]

15 **Frechen S**, Junge L, Saari TI, Suleiman AA, Rokitta D, Neuvonen PJ, Olkkola KT, Fuhr U. A semiphysiological population pharmacokinetic model for dynamic inhibition of liver and gut wall cytochrome P450 3A by voriconazole. *Clin Pharmacokinet* 2013; **52**: 763-781 [PMID: 23653047 DOI: 10.1007/s40262-013-0070-9]

16 **Fortún J**, Martín-Dávila P, Sánchez MA, Pintado V, Alvarez ME, Sánchez-Sousa A, Moreno S. Voriconazole in the treatment of invasive mold infections in transplant recipients. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 408-413 [PMID: 12827536]

17 **Saini L**, Seki JT, Kumar D, Atenafu EG, Cole DE, Wong BY, Božović A, Brandwein JM. Serum voriconazole level variability in patients with hematological malignancies receiving voriconazole therapy. *Can J Infect Dis Med Microbiol* 2014; **25**: 271-276 [PMID: 25371690]

18 **Chu HY**, Jain R, Xie H, Pottinger P, Fredricks DN. Voriconazole therapeutic drug monitoring: retrospective cohort study of the relationship to clinical outcomes and adverse events. *BMC Infect Dis* 2013; **13**: 105 [PMID: 23442261 DOI: 10.1186/1471-2334-13-105]

19 **Racil Z**, Winterova J, Kouba M, Zak P, Malaskova L, Buresova L, Toskova M, Lengerova M, Kocmanova I, Weinbergerova B, Timilsina S, Rolencova M, Cetkovsky P, Mayer J. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. *Mycoses* 2012; **55**: 483-492 [PMID: 22429709 DOI: 10.1111/j.1439-0507.2012.02186.x]

20 **Driscoll TA**, Yu LC, Frangoul H, Krance RA, Nemecek E, Blumer J, Arrieta A, Graham ML, Bradfield SM, Baruch A, Liu P. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults. *Antimicrob Agents Chemother* 2011; **55**: 5770-5779 [PMID: 21968355 DOI: 10.1128/AAC.00531-11]

21 **Hamada Y**, Seto Y, Yago K, Kuroyama M. Investigation and threshold of optimum blood concentration of voriconazole: a descriptive statistical meta-analysis. *J Infect Chemother* 2012; **18**: 501-507 [PMID: 22231601 DOI: 10.1007/s10156-011-0363-6]

22 **Iwamoto T**, Monma F, Fujieda A, Nakatani K, Katayama N, Okuda M. Hepatic drug interaction between tacrolimus and lansoprazole in a bone marrow transplant patient receiving voriconazole and harboring CYP2C19 and CYP3A5 heterozygous mutations. *Clin Ther* 2011; **33**: 1077-1080 [PMID: 21802143 DOI: 10.1016/j.clinthera.2011.07.006]

23 **van Wanrooy MJ**, Span LF, Rodgers MG, van den Heuvel ER, Uges DR, van der Werf TS, Kosterink JG, Alffenaar JW. Inflammation is associated with voriconazole trough concentrations. *Antimicrob Agents Chemother* 2014; **58**: 7098-7101 [PMID: 25223994 DOI: 10.1128/AAC.03820-14]

24 **Hadi M**, Westra IM, Starokozhko V, Dragovic S, Merema MT, Groothuis GM. Human precision-cut liver slices as an ex vivo model to study idiosyncratic drug-induced liver injury. *Chem Res Toxicol* 2013; **26**: 710-720 [PMID: 23565644 DOI: 10.1021/tx300519p]

25 **Barchiesi F**, Mazzocato S, Mazzanti S, Gesuita R, Skrami E,

Fiorentini A, Singh N. Invasive aspergillosis in liver transplant recipients: epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. *Liver Transpl* 2015; **21**: 204-212 [PMID: 25348192 DOI: 10.1002/lt.24032]

26 **Chen J**, Yang Q, Huang J, Li L. Risk factors for invasive pulmonary aspergillosis and hospital mortality in acute-on-chronic liver failure patients: a retrospective-cohort study. *Int J Med Sci* 2013; **10**: 1625-1631 [PMID: 24151434 DOI: 10.7150/ijms.6824]

27 **Suzuki Y**, Tokimatsu I, Sato Y, Kawasaki K, Sato Y, Goto T, Hashinaga K, Itoh H, Hiramatsu K, Kadota J. Association of sustained high plasma trough concentration of voriconazole with the incidence of hepatotoxicity. *Clin Chim Acta* 2013; **424**: 119-122 [PMID: 23747486 DOI: 10.1016/j.cca.2013.05.025]

28 **Zhang S**, Pillai VC, Mada SR, Strom S, Venkataramanan R. Effect of voriconazole and other azole antifungal agents on CYP3A activity and metabolism of tacrolimus in human liver microsomes. *Xenobiotica* 2012; **42**: 409-416 [PMID: 22106961 DOI: 10.3109/00498254.2011.631224]

29 **Neofytos D**, Lombardi LR, Shields RK, Ostrander D, Warren L, Nguyen MH, Thompson CB, Marr KA. Administration of voriconazole in patients with renal dysfunction. *Clin Infect Dis* 2012; **54**: 913-921 [PMID: 22267716 DOI: 10.1093/cid/cir969]

30 **Qiu Z**, Ren H, Cen X, Ou J, Xu W, Wang M, Wang L, Dong Y, Li Y, Liu W, Sun Y, Liang Z, Wang Q. [Clinical investigation of reduced-dose voriconazole on primary prevention in invasive fungal disease after allogeneic hematopoietic stem cell transplantation]. *Zhonghua Xue Ye Xue Za Zhi* 2014; **35**: 577-580 [PMID: 25052595 DOI: 10.3760/cma.j.issn.0253-2727.2014.07.001]

31 **Hoekstra WJ**, Garvey EP, Moore WR, Rafferty SW, Yates CM, Schotzinger RJ. Design and optimization of highly-selective fungal CYP51 inhibitors. *Bioorg Med Chem Lett* 2014; **24**: 3455-3458 [PMID: 24948565 DOI: 10.1016/j.bmcl.2014.05.068]

P- Reviewer: Al-Shamma S, De Ponti F, Kamimura K, Sarli B, Sarli R
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