Effect of Proton Pump Inhibitor on Plasma Voriconazole Concentration in Thai Patients

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Background: *Voriconazole is an antifungal drug used for treatment of invasive aspergillosis. It is metabolized mainly via the cytochrome P450 isoenzymes CYP2C19, through which its enzymatic activity can be inhibited by proton pump inhibitors (PPI), especially omeprazole. Previous reports demonstrated that omeprazole might be used to boost plasma voriconazole levels in infected patients. However, there was no difference in plasma voriconazole concentration in healthy individuals, who received omeprazole versus placebo. Therefore, the interaction between PPI and voriconazole may be different between healthy and infected individuals.*
Objective: *To determine the effects of omeprazole on plasma voriconazole concentration in Thai patients who had invasive fungal diseases.*
Material and Method: *The present study is a prospective observational study and is a sub-study of the voriconazole therapeutic drug monitoring study. Patients treated with voriconazole admitted at Siriraj Hospital during July 2011 to September 2013 were enrolled. Blood samples were drawn for plasma voriconazole concentration assays at day 0, 3, 7, 14 and 28. Data regarding PPI use were collected and analyzed in correlation with plasma voriconazole concentration.*
Results: *Of 54 patients enrolled, 47 had sufficient clinical data but 46 patients had complete data of voriconazole levels. Patients mean age was 47 years and 60% were male. Thirty-nine patients (83%) had invasive pulmonary aspergillosis. Forty-one patients (87.2%) received PPI, among which 37 (90.2%) were omeprazole. Patients with PPI use had no difference in plasma voriconazole concentration, when compared with those without PPI 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.*
Conclusion: *Omeprazole does not affect plasma voriconazole concentration in infected patients. However, patients who received higher doses of omeprazole (>20 mg/day) tend to have a higher concentrations of plasma voriconazole.*

Keywords: *Voriconazole, Proton pump inhibitor, Omeprazole, Drug interaction*

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Voriconazole is a second-generation triazole derived from fluconazole, which exhibits enhanced antifungal spectrum, compared with older triazoles. It is the drug of choice for treatment of invasive aspergillosis and other mold infections such as scedosporiasis and fusariosis[1,2]. Voriconazole is extensively metabolized via the cytochrome (CYP) P450 system, mainly by the CYP2C19 isoenzyme, and to a lesser extent via CYP2C9 and CYP3A4[3]. Therefore, the potential for drug interactions with voriconazole is high. Inducers of CYP450, such as rifampicin, long-acting barbiturates, and carbamazepine, decrease voriconazole concentrations. In contrast, CYP450 inhibitors, such as statins, benzodiazepines, calcium channel blockers, sulfonylureas, vinca alkaloids or proton pump inhibitors, especially omeprazole, increased blood voriconazole concentration. Voriconazole is available in both intravenous and oral formulations; the bioavailability of the oral drug is >90%[1]. Therapeutic drug range of voriconazole trough

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plasma concentrations is 1-5.5 mg/L and the levels more than 5.5 mg/L were correlated with toxicity[4,5]. The most common side effect is reversible disturbance of vision (photopsia) that occurs approximately 30%. Other common adverse reactions include skin rash and hepatitis[6].

Omeprazole, a widely available proton pump inhibitor (PPI), is indicated for duodenal and gastric ulcers, erosive esophagitis, and gastroesophageal reflux disease, acts by inhibition of gastric acid secretion[7]. Omeprazole is a competitive inhibitor of the CYP2C19 enzyme and it interacts with a number of drugs metabolized via the CYP450 system, including diazepam, phenytoin and warfarin. Omeprazole may increase the level of these drugs[8].

As mention above, voriconazole is metabolized mainly via the cytochrome P450 isoenzymes CYP2C19, through which its enzymatic activity can be inhibited by a PPI, especially omeprazole. Previous reports demonstrated that omeprazole may be used to boost plasma voriconazole levels in infected patients who had sub-therapeutic plasma voriconazole concentration[9]. However, there was no difference in plasma voriconazole concentration in healthy individuals, who received omeprazole versus placebo[10]. The authors hypothesized that the interaction between PPI and voriconazole may be different between healthy and infected individuals.

Material and Method

Patients

The inclusion criteria were patients aged ≥18 years, diagnosed invasive fungal disease and treated with voriconazole, who were admitted at Siriraj Hospital during July 2011 to September 2013.

Study design

This is a prospective observational study. Blood samples were drawn at day 0, 3, 7, 14 and 28 for trough voriconazole plasma concentration assays, using high performance liquid chromatography (HPLC) method[11]. Patients were followed-up for 90 days. All patients received oral voriconazole loading dose of 400 mg twice the first day, followed by 200 mg twice daily thereafter. In severe cases, patients may receive intravenous voriconazole initially depending on the attending physicians. Data collection includes basic characteristics such as age, body weight, sex, comorbid conditions, diagnosis, major organ involvement, criteria for diagnosis, laboratory tests and dose of voriconazole. Data regarding PPI use were collected, including indication for PPI use, type, dose, route and duration of PPI use. PPI data were analyzed in correlation with plasma voriconazole concentration.

Statistical analysis

Data are presented as mean and standard deviations, or median and range, for quantitative variables, and as absolute and relative frequencies for qualitative variables. Chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U test were used for statistical evaluation, where appropriate. All tests were two-sided and the threshold for statistical significance was established at a p-value <0.05. The statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Fifty-four patients were enrolled in the study, but only 47 had sufficient clinical data and 46 patients had complete data of voriconazole levels. Seven patients were excluded from the study due to adverse drug effect, refusal to continue study, and wrong diagnosis. The mean age was 47 (16-83) years and 59.6% were male. Baseline demographic and clinical features, including comorbid conditions, are summarized in Table 1.

Forty-five (95.7%) were diagnosed with invasive aspergillosis and two patients with fusariosis. The most common organ involvement was lung as

Table 1. Baseline demographic and clinical characteristics of 47 patients in this study

	n (%)
Age (year)	
Mean ± SD	47.0±14.3
Range	16-83
Sex	
Male	29 (59.6)
Body weight (kg)	
Mean ± SD	58.1±13.3
Co-morbid conditions*	
Hematologic malignancy	39 (83.0)
Solid tumor	1 (2.1)
Autoimmune	1 (2.1)
Post-transplant	3 (6.4)
Diabetes mellitus	4 (8.5)
Pre-cardiac condition	2 (4.3)
Chronic liver disease	3 (6.4)

* Some patients had >1 comorbidity
Unless indicated, all data are presented in proportion

Table 2. Diagnosis and major organ involvement and voriconazole dose in 47 patients

	n (%)
Diagnosis of invasive fungal disease	
Invasive aspergillosis	45 (95.7)
Fusariosis	2 (4.3)
Major organ involvement	
Pulmonary	39 (83.0)
Sinonasal	5 (10.6)
Skin and soft tissue	1 (2.1)
Disseminated	2 (4.3)
Criteria for invasive fungal diseases (EORTC/MSG)	
Proven	8 (17.0)
Probable	25 (53.2)
Possible	14 (29.8)
Voriconazole dose (mg)	
Loading dose (mg/kg/dose), mean ± SD	7.23±1.86
Treatment dose (mg/kg/dose), mean ± SD	3.59±0.93

Unless indicated, all data are presented in proportion

Table 3. Characteristic of proton pump inhibitor use

	n (%)
PPI use prior to voriconazole	42 (89.4)
Median (days)	20
Range (days)	1-180
Concurrent use of PPI and voriconazole	41 (87.2)
Median (days)	51
Range (days)	4-300
Indication for PPI use	
Prophylaxis for gastrointestinal bleeding	24 (58.5)
Thrombocytopenia/coagulopathy	5 (12.2)
Others	12 (29.3)
Type of PPI	
Omeprazole	37 (90.3)
Esomeprazole	2 (4.9)
Lansoprazole	1 (2.4)
Rabeprazole	1 (2.4)
Dose of PPI (mg)	
Mean dose ± SD	32.4±14.6
Route of PPI	
Oral	36 (87.8)
Intravenous	5 (12.2)

PPI = proton pump inhibitor
Unless indicated, all data are presented in proportion

found in 39 patients (83%). Proportions of patients diagnosed by EORTC/MSG for invasive fungal diseases and the voriconazole dose are summarized in Table 2.

A history of PPI use prior to voriconazole therapy was found in 42 patients (89.4%) and 41 (87.2%) had concurrent PPI and voriconazole use. Of the 42 patients who had PPI use, 37 (90.2%) of those used omeprazole. The median duration of PPI use prior to voriconazole prescription and the duration of concurrent PPI and voriconazole use were 20 (1-180) days and 51 (4-300) days, respectively. Data related to PPI use are summarized in Table 3.

When compared the median plasma voriconazole concentration in patients with and without PPI use, there was no difference 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, $p = 0.314$) as shown in Table 4, Fig. 1. During the first week of treatment, plasma voriconazole concentration in both groups tends to be high as in Fig. 1.

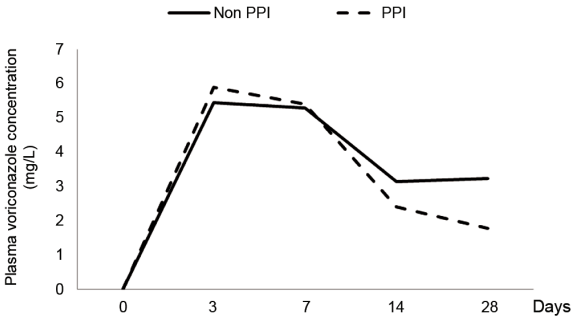
Although there was a trend toward higher plasma voriconazole concentration in patients receiving higher omeprazole dose (>20 mg/day), the difference of median voriconazol concentrations between those treated with high (>20 mg/day) and low (20 mg/day) doses of omeprazole was not statistically significant 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, $p = 0.154$), as shown in Fig. 2.

The authors also analyzed the effect of duration of omeprazole use on plasma voriconazole

Table 4. Median and range of plasma voriconazole concentration in each PPI group in 46 patients

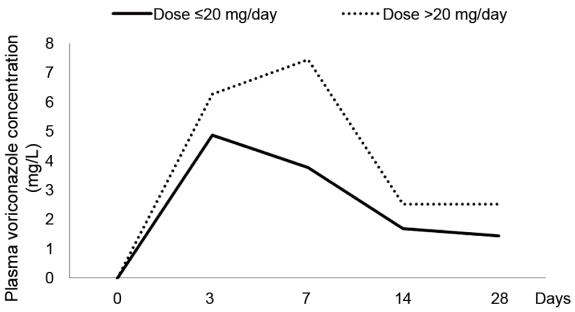
	Plasma voriconazole concentration (mg/L), median (range)				
	Day 0	Day 3	Day 7	Day 14	Day 28
All group (n = 46)	0	5.64 (0.79-17.75)	5.35 (0-24.0)	2.55 (0.10-21.62)	2.23 (0-8.31)
Non PPI group (n = 6)*	0	5.44 (3.09-7.63)	5.29 (0-8.24)	3.13 (1.97-7.46)	3.23 (0.41-6.63)
PPI group (n = 40)*	0	5.89 (0.79-17.75)	5.40 (4.45-24.0)	2.40 (0.10-21.62)	1.77 (0-8.31)
Omeprazole group (n = 37)	0	5.25 (0.79-17.03)	5.22 (0.44-15.62)	2.38 (0.10-13.98)	1.74 (0-8.31)

* p-value between non PPI and PPI group at day 3, 7, 14 and 28 were 0.744, 0.471, 0.372 and 0.314, respectively



p-value at day 3, 7, 14 and 28 were 0.744, 0.471, 0.372 and 0.314, respectively

Fig. 1 comparison of voriconazole concentration in patients with and without PPI.



p-value at day 3, 7, 14 and 28 were 0.429, 0.166, 0.534 and 0.154, respectively

Fig. 2 Comparison of plasma voriconazole level in patients receiving omeprazole ≤20 mg/day and >20 mg/day.

concentration. There was no difference in plasma voriconazole concentration between patients in association with omeprazole duration, whether omeprazole was prescribed prior to or concurrent with voriconazole for 7, 14 or 30 days.

Discussion

Several factors have been shown to affect plasma voriconazole concentration, such as drug-drug interactions, polymorphisms of the gene encoding the CYP2C19 enzyme[12-15], liver diseases and age[5,16]. In hematological patients, one of the drugs commonly prescribed in concurrence with voriconazole is omeprazole, a competitive CYP2C19 inhibitor. In the present study, the authors collected data in patients with invasive fungal diseases and the association between omeprazole and plasma voriconazole concentration was not demonstrated. These results are similar to those from a study by Wood et al in which the omeprazole had no clinically relevant effect on voriconazole exposure[10]. However, that study was evaluated in healthy male volunteers aged 18-45 years[10].

Our findings may be due to the majority of patients receiving omeprazole as a routine prescription and in the standing orders for hematological malignancy protocol. In addition, other drug-drug interactions and liver function in each patient may play some roles. Greater sample size is needed to demonstrate the effect of omeprazole on voriconazole concentration. Nevertheless, the plasma voriconazole concentration tends to be higher in those receiving high dose omeprazole (>20 mg/day) compared with the low dose group (≤20 mg/day).

In summary, although the co-administration of omeprazole does not affect plasma voriconazole concentration in infected patients, patients who received higher dose omeprazole (>20 mg/day) tend to have a higher level of plasma voriconazole, especially during the first week. From the present study, the authors therefore recommend that therapeutic drug monitoring of plasma voriconazole concentration should be performed in patients who concurrently receive more than 20 mg/day omeprazole.

What is already known on this topic?

Voriconazole is metabolized via CYP2C19 and omeprazole is a CYP2C19 inhibitor. So, there may be interactions between voriconazole and a proton pump inhibitor.

What this study adds?

Although omeprazole does not significantly affect plasma voriconazole concentration in infected patients, those who received higher doses of omeprazole tend to have a higher concentrations of plasma voriconazole.

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Potential conflicts of interest

This research received an award from Pfizer INSPIRE program.

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ผลของยายับยั้งการขับโปรตอนต่อระดับยาวอริโคนาโซลในผู้ป่วยไทย

เมธี ชยะกุลคีรี, ณัฏฐนันท์ ภูวิภิรมย์, พิมพ์กมล เสียงวัฒนะ, มณฑิรา มณีรัตนะพร

ภูมิหลัง: *วอริโคนาโซลเป็นยาต้านเชื้อรา ที่แนะนำให้ใช้รักษาโรคติดเชื้อราแอสเปอร์จิลลัสชนิดรุกราน ยานี้มีเมตาบอลิสมผ่านทางเอนไซม์ไซโตโครมพี 450 ไอโซเอนไซม์ CYP2C19 ซึ่งถูกยับยั้งได้โดยยากลุ่มยับยั้งการขับโปรตอนโดยเฉพาะยาโอเมพราโซล ซึ่งเคยมีผู้ใช้ยานี้เพื่อเพิ่มระดับยาวอริโคนาโซลในผู้ป่วยติดเชื้อ การศึกษาก่อนหน้านี้พบว่ายาโอเมพราโซลไม่มีผลต่อระดับยาวอริโคนาโซล แต่เป็นการศึกษาในคนปกติโดยยังไม่เคยมีการศึกษาในผู้ป่วยที่ติดเชื้อราชนิดรุกราน ซึ่งอาจมีผลต่อระดับยาในพลาสมาแตกต่างจากคนปกติ*

วัตถุประสงค์: *เพื่อศึกษาผลของยายับยั้งการขับโปรตอนต่อระดับยาวอริโคนาโซลในผู้ป่วยติดเชื้อราชนิดรุกราน*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบสังเกตไปข้างหน้าและเป็นการศึกษาย่อยของโครงการศึกษา การตรวจวัดระดับยาวอริโคนาโซลเพื่อการรักษา เป็นการศึกษาในผู้ป่วยติดเชื้อราชนิดรุกรานที่ได้รับยาวอริโคนาโซลที่รับไว้รักษาในโรงพยาบาลศิริราช ระหว่างเดือนกรกฎาคม พ.ศ. 2555 ถึง กันยายน พ.ศ. 2557 โดยผู้ป่วยจะได้รับการเจาะเลือดตรวจระดับยาวอริโคนาโซลในวันที่ 0, 3, 7, 14, 28 และเก็บข้อมูลที่เกี่ยวข้องกับการใช้ยายับยั้งการขับโปรตอน โดยปัจจัยที่สัมพันธ์กับระดับยาจะถูกนำไปวิเคราะห์*

ผลการศึกษา: *ในผู้ป่วย 54 ราย มี 47 ราย ที่มีข้อมูลทางคลินิกครบถ้วน แต่มี 46 ราย ที่มีข้อมูลระดับยาในเลือดครบถ้วน อายุเฉลี่ยของผู้ป่วยคือ 47 ปี โดยส่วนใหญ่เป็นเพศชายประมาณร้อยละ 60 ผู้ป่วย 39 ราย (ร้อยละ 83) ติดเชื้อแอสเปอจิลลัสในปอด มีผู้ป่วย 41 ราย (ร้อยละ 87.2) ได้รับยายับยั้งการขับโปรตอน โดยในกลุ่มที่ได้รับยายับยั้งการขับโปรตอนเป็นโอเมพราโซล 37 ราย (ร้อยละ 90.2) ผลการศึกษาพบว่ายายับยั้งการขับโปรตอนไม่มีผลต่อระดับยาวอริโคนาโซล เมื่อเทียบกับกลุ่มที่ไม่ได้ยายับยั้งการขับโปรตอน ในวันที่ 3 (5.89 และ 5.44 มก./ลิตร ค่าพี 0.744), วันที่ 7 (5.4 และ 5.29 มก./ลิตร ค่าพี 0.471), วันที่ 14 (2.40 และ 3.13 มก./ลิตร ค่าพี 0.372) และวันที่ 28 (1.77 และ 3.23 มก./ลิตร ค่าพี 0.314) อย่างไรก็ตามผู้ป่วยที่ได้รับยาโอเมพราโซลในขนาดมากกว่า 20 มก./วัน มีระดับยาวอริโคนาโซลสูงกว่าผู้ป่วยที่ได้รับน้อยกว่าหรือเท่ากับ 20 มก./วัน แต่ไม่มีนัยสำคัญทางสถิติ ทั้งในวันที่ 3 (6.27 และ 4.87 มก./ลิตร ค่าพี 0.429), วันที่ 7 (7.44 และ 3.78 มก./ลิตร ค่าพี 0.166), วันที่ 14 (2.52 และ 1.68 มก./ลิตร ค่าพี 0.534) และวันที่ 28 (2.51 และ 1.44 มก./ลิตร ค่าพี 0.154) นอกจากนี้ระยะเวลาที่ได้รับยาโอเมพราโซลก่อน หรือ ร่วมกับยาวอริโคนาโซลไม่มีผลต่อระดับยาวอริโคนาโซลในพลาสมาผู้ป่วย*

สรุป: *ยาโอเมพราโซลไม่มีผลต่อระดับยาวอริโคนาโซลในพลาสมาผู้ป่วย อย่างไรก็ตามผู้ป่วยที่ได้รับยาโอเมพราโซลในขนาดมากกว่า 20 มก./วัน มีแนวโน้มที่จะมีระดับยาวอริโคนาโซลที่สูงกว่า*