Original Article

ความปลอดภัยของการใช้ยา Voriconazole ในผู้ป่วยชาวไทย: การศึกษาเชิงพรรณนาแบบย้อนหลัง

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Safety Profile of Voriconazole in Thai Patients: A Retrospective, Descriptive Study.

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บทคัดย่อ:

วัตถุประสงค์: เพื่อหาความชุกและรูปแบบของอาการไม่พึงประสงค์จากการใช้ยา voriconazole ในผู้ป่วยชาวไทย

วัสดุและวิธีการ: ทำการศึกษาเชิงพรรณนาแบบย้อนหลังในผู้ป่วยในที่ได้รับยา voriconazole ณ โรงพยาบาลรามาธิบดี ระหว่างวันที่ 1 กรกฎาคม พ.ศ. 2548 ถึง 31 มีนาคม พ.ศ. 2551 โดยการทบทวนเวชระเบียน เพื่อค้นหาเหตุการณ์ไม่พึงประสงค์ของยา เภสัชกรคลินิกและแพทย์ประเมินอาการไม่พึงประสงค์จากยา voriconazole ด้วย Naranjo's algorithm จัดกลุ่มอาการไม่พึงประสงค์จากยาตามระบบอวัยวะโดยอาศัยเกณฑ์ขององค์การอนามัยโลก และประเมินความชุก ระยะเวลาเริ่มเกิดและระยะเวลาที่เกิดอาการไม่พึงประสงค์ ความรุนแรงและผลลัพธ์ของอาการไม่พึงประสงค์

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ผลการศึกษา: ผู้ป่วยได้รับการประเมินทั้งหมด 128 ราย (ชาย 62 ราย หญิง 66 ราย) มีการใช้ voriconazole 162 ครั้ง โดยที่ผู้ป่วย 94 ราย เกิดอาการไม่พึงประสงค์จากยา voriconazole 114 ครั้ง คิดเป็นความชุกของอาการไม่พึงประสงค์ร้อยละ 70.4 ระบบอวัยวะที่เกิดอาการไม่พึงประสงค์มากที่สุดคือ ตับและน้ำดี (ร้อยละ 54.6) มีลักษณะเป็น cholestatohepatitis, cholestatic jaundice ค่าการทำงานของตับเพิ่มขึ้น transaminitis และ hyperbilirubinemia รองลงมา คือ ความผิดปกติในระบบการเผาผลาญและโภชนาการ (ร้อยละ 17.3) ส่วนความผิดปกติในระบบประสาทส่วนกลางและส่วนปลาย พบร้อยละ 2.2 ขณะที่การรบกวนการมองเห็น และผื่นผิวหนังพบน้อย

สรุป: ความชุกของอาการไม่พึงประสงค์จากการใช้ยา voriconazole พบได้สูง ระบบอวัยวะที่เกิดอาการไม่พึงประสงค์มากที่สุดคือ ตับและน้ำดี แม้ว่าอาการไม่พึงประสงค์ส่วนใหญ่สามารถหายได้และไม่เป็นอันตรายถึงชีวิต การเฝ้าระวังและติดตามอาการไม่พึงประสงค์ยังมีความจำเป็นในผู้ป่วยที่ใช้ยา voriconazole

คำสำคัญ: ข้อมูลความปลอดภัย, อาการไม่พึงประสงค์, voriconazole

Abstract:

Objective: To determine the prevalence and profile of adverse drug reactions (ADRs) of voriconazole in Thai patients.

Material and Method: A retrospective, descriptive study was conducted in in-patients who received voriconazole at Ramathibodi Hospital during the period of 1st July 2005 to 31st March 2008. Patients' profiles were reviewed for adverse drug events (ADEs) of voriconazole. The causality assessment of ADRs was performed by a clinical pharmacist and a physician using Naranjo's algorithm. ADR data were classified based on system-organ classification arranged by WHO Collaborating Centre for International Drug Monitoring. Prevalence, onset, duration and severity as well as outcome of ADRs were determined.

Results: One hundred and twenty-eight patients' profiles (62 males, 66 females) were assessed with 162 voriconazole use episodes. In total, 94 patients had ADRs from 114 voriconazole use episodes. The prevalence of ADR was therefore 70.4%. ADRs were mostly expressed as liver and biliary system disorders (54.6%). These included the pattern of cholestatohepatitis, cholestatic jaundice, increased liver function tests (LFTs), transaminitis and hyperbilirubinemia. The second most common ADRs were metabolic and nutritional disorders (17.3%). Disorders in central and peripheral nervous systems were observed in 2.2% while visual disturbances and skin rash were less common.

Conclusion: High prevalence of ADRs of voriconazole was revealed. Liver and biliary system disorders were the most frequent ADRs found. Even though most ADRs could be recovered and were not life-threatening, careful detection and monitoring of ADRs are still required for voriconazole-treated patients.

Keywords: adverse drug reaction, safety profile, voriconazole

Introduction

Voriconazole, a broad-spectrum triazole antifungal agent, has been introduced for the treatment of life-threatening fungal infections for approximately a decade.[1] Although generally well tolerated, voriconazole may cause several common adverse drug reactions (ADRs), for example, transient visual disturbances, hepatotoxicity and skin rashes.[2] Other less commonly observed ADRs are hyperkalemia and hypoglycemia.[3] However, it is not known whether these reactions are associated with higher cumulative doses of the drug. Furthermore, some patients receiving intravenous voriconazole may develop adverse effects, e.g., hypoglycemia, electrolyte disturbances, and, possibly, confusion and pneumonitis without any remarkable abnormal alterations in liver function tests (LFTs).[1,4-7]

Accordingly, different patterns of ADRs in patients receiving voriconazole have been found in clinical practices. It seems that hepatotoxicity is the most common ADR indicated by elevation of LFTs[8-11] but electrolyte disturbances have also been found in the highest incidence in one study.[12] Furthermore, hepatotoxicity affects the treatment decision such as dose regimen of concomitant medication and drug of choice. These reports suggest that ADRs of voriconazole are unpredictable and inconsistent. Several factors may contribute to high incidences of ADR including multiple drug interactions.

Presently, there is no report on voriconazole safety in Asians. For this reason, the present study was performed to determine the prevalence of ADRs of voriconazole in inpatients at Ramathibodi Hospital, a university hospital in Thailand.

Material and Method

A retrospective, descriptive study was conducted. The study protocol was approved by the Human Research Ethic Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand (MURA2550/421). Profiles of inpatients who were treated with voriconazole at Ramathibodi Hospital during the period of 1st July 2005 to 31st March 2008 were reviewed. Inclusion criteria were inpatients of all ages who received voriconazole via intravenous (IV) and/or oral routes as prophylactic, empirical, pre-emptive or targeted treatment. Prophylactic treatment was defined as the preventive administration of an antifungal agent to patients at risk of an invasive fungal infection (IFI) without attributable signs and symptoms while empirical treatment was defined as the initiation of antifungal treatment in patients at high risk of an IFI with established clinical signs and symptoms, but without pathogen identification. In contrast, pre-emptive treatment was defined as the initiation of antifungal treatment in patients at high risk of an IFI with established surrogate markers, i.e. serum galactomannan, radiographic signs and/or laboratory tests but without definitive verification by histopathology and/or culture of the causal pathogen and targeted treatment was defined as the initiation of antifungal treatment only if diagnostic criteria allowing pathogen identification, i.e. culture from a physiologically sterile site or histopathological evidence of an IFI.[13]

Patient's demographic data, history of drug allergy, primary underlying diseases, concurrent medications, complementary and alternative medication intake were collected. Focusing on voriconazole

use, indication, route of administration, dosage (mg/day), duration of use, monitoring parameters, laboratory tests and drug interaction were reviewed in order to investigate for adverse drug events (ADEs) from voriconazole. Causality assessment of ADRs by the Naranjo probability scale was performed by a clinical pharmacist and a physician. If the agreement of ADR causality assessments between clinical pharmacist and physician was classified as possible, probable or definite, then the patient was concluded to have ADR from voriconazole. The prevalence of ADRs was thus determined. ADR data were classified based on system-organ classification arranged by WHO Collaborating Centre for International Drug Monitoring. Severity of ADRs and patient outcomes were categorized according to the modified guidelines for reporting suspected adverse events caused by health products, Food and Drug Administration, Ministry of Public Health, Thailand.[14] Three levels were categorized for the severity of ADRs. Level A was given if the ADR suspiciously led to death of the patient. Level B was given if the ADR occurred while the patient's life was threatened. Level C was given if the ADR led to the patient's prolonged hospitalization. Patient outcome was categorized into 5 levels. Level I was the patient who recovered completely after ADR occurred, level II was the patient who recovered partially after ADR occurred, level III was the patient who did not recover after ADR occurred, level IV was the patient who died, attributable to other causes such as patients' disease, and level V was no information on the outcome after the ADR occurrence. Regarding liver toxicity, LFTs values including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TB), and direct bilirubin (DB) were recorded and classified according to the National Cancer Institute (NCI) Common Terminology Criteria (CTC version 2.0) (http://ctep.cancer.gov). LFT abnormalities were included in liver and biliary system disorders when liver function grades increased at least 1 grade from baseline. Patient's demographic data and information on voriconazole use including indication, route of administration, dosage (mg/day), and duration of use were analyzed by descriptive statistics. Categorical data were presented as frequency and percentage whereas numerical data were presented as frequency, percentage, and mean±S.D. Evidence of ADRs was presented as prevalence.

Results

In total, 172 voriconazole-treated patients satisfied the inclusion criteria. However, three of them were excluded because the order of voriconazole was stopped before the first dose was given to the patients while another 41 patients were excluded because their medical records were missing. Therefore, data from 128 patients (62 males and 66 females) with 162 voriconazole use episodes were reviewed in order to investigate ADEs from voriconazole use. The results of ADR causality assessment revealed that 94 voriconazole-treated patients with 114 voriconazole use episodes had ADRs from voriconazole. Accordingly, the prevalence of ADRs was 70.4%.

The demographic and clinical characteristics of the 94 patients which included about 20% of children with 114 voriconazole use episodes were shown in Table 1. The median age (range) was

37.50 (0.08-83) years and the median body mass index, BMI (range) was 18.96 (9.00-32.46) kg/m^2. Voriconazole was used primarily as pre-emptive treatment (45.6%) with the median duration (range) of voriconazole use of 15 days (range 1-632 days). The median loading and maintenance doses (range) of voriconazole were 600 mg (range 60-1,080 mg) and 400 mg/day (range 50-800 mg/day), respectively. The major cause of fungal infection was pulmonary aspergillosis. Moreover, some patients concomitantly took voriconazole with other medications such as cyclosporin, tacrolimus, phenytoin, omeprazole and warfarin.

Table 1 Demographic and clinical characteristics of voriconazole-treated patients.

Characteristics	No. of patients (n=94)
Female, n (%)	51 (54.0)
Child (<12 years), n (%)	20 (21.3)
Underlying disease, n (%)	
Acute leukemia	35 (37.2)
Lymphoma	9 (9.5)
Other non-hematological cancer	18 (19.1)
Solid tumors	9 (9.5)
Stem cell transplantation	9 (9.5)
Solid-organ transplantation	4 (4.2)
AIDS	1 (1.0)
Metabolic diseases	20 (21.2)
Cardiovascular diseases	16 (17.0)
Renal diseases	14 (14.8)
Autoimmune diseases	14 (14.8)
Neurological diseases	7 (5.4)
Gastrological diseases	4 (4.2)
Others[a]	12 (12.7)
Voriconazole indication[b], n (%), n=114	
Prophylactic therapy	1 (0.9)
Pre-emptive	52 (45.6)
Treatment	
Empirical	12 (10.5)
Targeted	49 (43.0)
Fungi involved[b], n (%)	
Aspergillus spp.	30 (26.3)
Fusarium spp.	4 (3.5)
Yeasts	
C. albicans	4 (3.5)
Non-albicans candida[c]	9 (7.9)
≥2 *Candida* spp.	1 (0.9)
Site of infection[b], n (%)	
Pulmonary	90 (78.9)
Sinus	6 (5.3)
Cerebral	4 (3.5)
Disseminated (excluded cerebral involvement)	12 (10.5)
Others[d]	6 (5.3)

[a]Other underlying diseases were allergic bronchitis, allergic rhinitis, benign prostate hypertrophy (BPH), cataract, deep vein thrombosis (DVT), Down syndrome, chronic obstructive pulmonary disease (COPD), gouty arthritis, hemorrhoid, microscopic polyangiitis, osteoarthritis, severe combined immunodeficiency disease (SCID).

[b]In 94 patients, there were 114 voriconazole uses.

[c]Non-albicans candida included *C. tropicalis*, *C. parapsilosis*, *C. glabata* and *C. krusei*.

[d]Other sites were eye, mediastinum, trachea, urinary tract and oropharyngeal tissues.

Table 2 Characteristics of ADRs, organ system affected, classified by the criteria of WHO Collaborating Centre for International Drug Monitoring.

Type of ADRs	No. of ADRs (%) n=185	Median onset of ADR, (range) days	Median time for disappearance of ADR, (range) day	Severity[d], No. of episodes (%)	Outcome[e], No. of episodes (%)
1. Liver and biliary system disorders	101 (54.6)	9 (1-206)	20 (1-262)	A: 0 B: 1 (1) C: 23 (23)	I: 34 (34) II: 14 (14) III: 11 (10) IV: 21 (21) V: 21 (21)
2. Metabolic and nutritional disorders	32 (17.3)	4 (1-53)	6 (1-178)	A: 0 B: 0 C: 8 (25)	I: 6 (18) II: 2 (7) III: 0 IV: 16 (50) V: 8 (25)
3. Blood disorders	10 (5.4)	5 (1-25)	5.50 (3-35)	A: 0 B: 0 C: 4 (40)	I: 2 (20) II : 0 III: 1 (10) IV: 5 (50) V: 2 (20)
4. Urinary system disorders	10 (5.4)	4 (2-17)	7 (1-15)	A: 0 B: 0 C: 5 (50)	I: 4 (40) II: 2 (20) III: 0 IV: 3 (30) V: 1 (10)
5. Cardiovascular disorders	7 (3.8)	4 (1-12)	9 (1-29)	A: 0 B: 2 (29) C: 3 (43)	I: 2 (28) II: 1 (16) III: 0 IV: 4 (56) V: 0
6. Endocrine disorders	6 (3.2)	5 (1-6)	2 (1-7)	A: 0 B: 0 C: 2 (33)	I: 2 (33) II: 1 (17) III: 0 IV: 3 (50) V: 0
7. Gastrointestinal disorders	6 (3.2)	4.50 (1-14)	3 (1-10)	A: 0 B: 0 C: 2 (33)	I: 4 (66) II: 1 (17) III: 0 IV: 1 (17) V: 0

Table 2 (Continued)

Type of ADRs	No. of ADRs (%) n=185	Median onset of ADR, (range) days	Median time for disappearance of ADR, (range) day	Severity[d], No. of episodes (%)	Outcome[e], No. of episodes (%)
8. Central and peripheral nervous system disorders	4 (2.2)	4 (2-6)	2.50 (1-4)	A: 0 B: 0 C: 1 (25)	I: 1 (25) II: 0 III: 1 (25) IV: 0 V: 2 (50)
9. Body as a whole-general disorders	3 (1.6)	1 (1-32)	2[a]	A: 0 B: 0 C: 1 (33)	I: 2 (67) II: 0 III: 0 IV: 1 (33) V: 0
10. Respiratory system disorders	3 (1.6)	4 (1-42)	1[b]	A: 0 B: 0 C: 3 (100)	I: 1 (33) II: 0 III: 0 IV: 2 (67) V: 0
11. Vision disorders	2 (1.1)	2 (1-3)	5 (2-8)	A: 0 B: 0 C: 0	I: 2 (100) II: 0 III: 0 IV: 0 V: 0
12. Skin and appendage disorders	1 (0.5)	11	-[c]	A: 0 B: 0 C: 0	I: 0 II: 0 III: 0 IV: 0 V: 1 (100)

[a]There were 2 patients whose ADRs were recovered and time for disappearance of ADR were 2 days, in both cases.

[b]There was only 1 patient whose ADR was recovered and time for disappearance of ADR was 1 day.

[c]There was only 1 patient who had ADR of skin and appendage disorders and the patient did not come to follow up so time for disappearance of ADR could not be assessed.

[d]Severity: Level A = the ADR suspiciously led to death of the patient, Level B = the ADR occurred while the patient's life was threatened, Level C = the ADR led to the patient's prolonged hospitalization.

[e]Outcome: I = the patient who recovered completely after ADR occurred, II = the patient who recovered partially after ADR occurred, III = the patient who did not recover after ADR occurred, IV = the patient who died, attributable to other causes such as patients' disease, V = no information on the outcome after the ADR occurrence.

A total of 185 ADRs were identified and classified by affected organ system as shown in Table 2. The most common ADR was found in liver and biliary system (54.6%) including cholestatohepatitis, cholestatic jaundice, increased LFTs, transaminitis and hyperbilirubinemia. The second most common ADRs were metabolic and nutritional disorders (17.3%). The ADRs in other systems occurred in less than or about 5%. Four ADRs (2.2%) classified in central and peripheral nervous system disorders including acute delirium, alteration of consciousness, delirium and hallucination were observed. Vision disorders (including color visual change and visual change) were found in two patients while skin and appendage disorders occurred in one patient. Most ADRs occurred after 4-5 days of voriconazole treatment and disappeared within 1 week up to almost 3 weeks. No ADRs suspiciously led to patients'death (severity level A), most led to prolonged hospitalization (severity level C). The outcomes varied from complete recovery to death from other causes.

Discussion

A total of 94 patients with 185 ADRs were found in this study. These ADRs were revealed in 114 voriconazole use episodes from the total of 162 voriconazole use episodes. The prevalence of ADRs was 70.4%. This was higher than the safety data of voriconazole reported in clinical practices which ranged from 8.3-47.5%.[9-12] However, it is difficult to directly compare the prevalence of ADRs in the present study with previous retrospective studies in clinical practices due to the discrepancies of ADR's definitions, method of ADR detection and studied population. Moreover, some studies only reported ADRs in a specific organ system. Our studied population's median age (range) was 37.50 (0.08-83) years which approximately 20% of them were children less than 12 years old. This showed that ADRs in our study occurred in younger patients compared to previous clinical controlled trials and clinical practices' population, whose ages ranged between 12-82 years with the median ages ranging between 46.3-52 years.[3,15,16] Moreover, our patients mostly suffered from malnutrition due to cancer or had immunocompromised status. This led to a low median BMI of 18.96 kg/m^2. The major site of infection in our studied population were the lungs which were mainly infected by *Aspergillus* spp. (26.3%). This might contribute to the condition with more severity in our studied population.

As mentioned, LFT abnormalities had the highest prevalence in our study. Liver and biliary system disorders were also the most frequently reported ADRs in previous clinical controlled trials and clinical practices with voriconazole use.[3,15,16] Our data combined with the previous reports suggest that the most common ADR of voriconazole is hepatotoxicity, therefore, patients treated with this drug should be monitored for liver function. The median onset of hepatotoxicity in our study manifested around day 9 of voriconazole use which was similar to a previous study by Denning, et al[3] who showed the onset within the first 10 days of treatment. However, the incidence of hepatotoxicity varied considerably between 3.6%-46.2% in different studied populations (adult patients with AIDS, immunocompromised children), different indications (empirical therapy versus treatment for proven invasive aspergillosis), the routes of administration

(IV versus oral) and dosages of voriconazole.[5-7,17-19] It was noticed that our study found the high prevalence of hepatotoxicity (54.6%). This might be because our study included patients who had various underlying diseases and higher baseline of LFTs whereas in previous clinical trials, these patients would be excluded from the studies if LFT values were higher than the upper limit of normal (ULN) for 2-5 times. Also, the major administration route was oral. These data suggested that high concentrations of voriconazole in the portal blood precipitate liver enzyme abnormalities.[19-21] The patients in the present study also concomitantly took voriconazole with other medications which could affect voriconazole metabolism such as cyclosporin, tacrolimus, phenytoin, omeprazole and warfarin. However, no ADR was associated with these drug interactions. Another reason might be due to the difference between races. In our study, the voriconazole-treated patients were entirely Asians while the population in earlier prospective clinical controlled trials[3,15,16] were mostly Caucasians. About 20% of Asian population are known to be poor metabolizers for CYP2C19 substrates.[3] Therefore, it's possible that Asian populations may have the potential to have higher voriconazole level and take higher risk for toxicity from voriconazole. Suan, et al[17] also suggested the need for caution when commencing voriconazole in patients with CYP2C19 polymorphisms and therapeutic drug monitoring is important in such cases.

Our study showed that the median time for the disappearance of hepatotoxicity was 20 days. This implies that abnormal LFTs are reversible and hepatotoxicity can be resolved and also suggests that voriconazole can be reintroduced if the benefits outweigh the risks even though a high incidence of hepatotoxicity was demonstrated. Only 24% of patients with hepatotoxicity led to prolonged hospitalization since they partially recovered or did not recover after the occurrence of ADR, while many (34%) recovered completely.

The second most common ADRs were metabolic and nutritional disorders which included hypercalcemia, hyperchloremia, hypokalemia, hyperkalemia, hypomagnesemia, hyponatremia and hypernatremia. This is different from the other report.[3] The mechanism is still unclear. We suggest that this finding should be further investigated in prospective study and closed monitoring of electrolytes and voriconazole level should be performed.

Another interesting finding was voriconazole-induced central and peripheral nervous system disorders which were mostly presented in elderly patients. The median (range) age of our studied population who had these ADRs was 70.50 (43-83) years which was similar to previous reports.[4,18,19] This might support the finding that serum voriconazole levels in elderly population (>65 years) tend to be higher than those in patients aged 45 years or less.[20]

For visual disturbances, the present study revealed these ADRs in only 1.1%. Even though these ADRs were the most common in clinical trials, occurring in about 30% of patients[7] or 18% reported in the French Pharmacovigilance Database.[4] This might be because these ADRs were transient and fully reversible hence the patients did not complain and rarely required drug discontinuation. Furthermore, objective visual examination was not routinely performed. Consequently, these ADRs were rarely detected in our study.

Other reported ADRs in the present study included decreased creatinine clearance (CrCL) (5.4%), hematologic disorders (5.4%) and cardiovascular disorders (3.8%), as found in other studies.[11,12] This might be because the present studied population was mostly hematological cancer patients (46.7%) and cardiovascular disorders (17%). Maculopapular rash was less common in the present study. It was observed in only one patient (0.5%) and not serious like Stevens-Johnson syndrome or toxic epidermal necrolysis, which has been reported in 1-5%.[1,5,21-25]

According to our knowledge, our study was the first report which focused on voriconazole safety in Asians. Moreover, the ADRs were confirmed by a clinical pharmacist and a physician. However, the study had some limitations. Firstly, it was a retrospective, descriptive study which was performed by chart review. Accordingly, some patients' information were missing and not complete. Secondly, data of 24% of studied population were missing. This was quite high, however, the prevalence of ADRs in our study was still higher than in other studies even though the comparison could not be performed directly. Thirdly, correlation between ADRs and voriconazole blood levels could not be concluded since no therapeutic drug monitoring was routinely performed during the study period. Therefore, we suggested that further investigation for ADRs should be performed as a prospective study and therapeutic drug monitoring may be required in patients who are treated with voriconazole. Target serum voriconazole levels between 1-5.5 μg/mL might be applied to increase the efficiency and safety of voriconazole treatment.[26-30]

Conclusion

The current study showed a high prevalence of ADRs from voriconazole use. Liver and biliary system disorders were the most frequent ADRs found, while visual disturbances and skin rash were less common. Most patients could recover within a certain period of time and most ADRs were not life-threatening. However, careful detection and monitoring of ADRs are still required to help improve the safety of voriconazole-treated patients.

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