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ORIGINAL ARTICLE

Retrospective Cohort Study

Remission of hepatotoxicity in chronic pulmonary aspergillosis patients after lowering trough concentration of voriconazole

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Abstract

BACKGROUND

Chronic pulmonary aspergillosis (CPA) is a rare syndrome that is often accompanied by gradual lung tissue destruction. Voriconazole is usually employed as the first-line agent for CPA treatment. However, some patients can develop hepatotoxicity and often were forced to stop voriconazole treatment.

AIM

To record the improving trend of liver function and the therapeutic effects in patients after lowering the trough concentration of voriconazole.

METHODS

This study retrospectively analyzed 12 adult CPA patients who developed hepatotoxicity during the voriconazole treatment. In these patients, the oral dose was reduced to 3/4 or 1/2 of the standard dose (4 mg/kg, twice daily), and the lower limit of voriconazole trough concentration was maintained more than 0.5 μg/mL. The trend of remission of liver toxicity after drug reduction in 12 patients was recorded. During the same period, 25 patients who received standard doses served as the control group. Data from the two groups were collected and analyzed for different parameters such as demographic characteristics, underlying pulmonary disorders, laboratory tests, and therapeutic effect. The differences between the two groups were statistically compared.

RESULTS

Hepatotoxicity occurred in 12 patients within 28-65 d after oral voriconazole

original anonymous dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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treatment. Hepatotoxicity was mainly manifested by the significantly increased level of gamma-glutamyltransferase and a slight increase of alanine aminotransferase and aspartate aminotransferase. The oral dose of voriconazole was reduced to approximately 3 mg/kg in seven patients and approximately 2 mg/kg in five patients. The average trough concentrations for the 12 patients before and after voriconazole oral dose reduction were 3.17 ± 1.47 μg/mL (1.5-6.0 μg/mL) and 1.70 ± 0.78 μg/mL (0.6-3.3 μg/mL), respectively (P = 0.02). After lowering the trough concentrations, the hepatotoxicity was alleviated in all the patients. However, gamma-glutamyltransferase levels declined slowly. After 4 mo of treatment, 7 of the 12 patients were successfully treated in the low trough concentrations group (41.7%). Similarly, 8 of the 25 patients in the standard treatment dose group (32.0%) were effectively treated. There was no statistical difference between the groups (P = 0.72).

CONCLUSION
Reducing the lower limit of the voriconazole trough concentration to 0.5 μg/mL can alleviate the hepatotoxicity and maintained certain clinical efficacy in CPA patients; however, patients should be closely monitored.

Key Words: Voriconazole; Hepatotoxicity; Chronic pulmonary aspergillosis; CYP2C19 genotypes; Reduction; Trough concentration

Core Tip: In this retrospective study, we evaluated 12 adult chronic pulmonary aspergillosis patients who developed hepatotoxicity during voriconazole treatment. The hepatotoxicity mainly manifested as a significant increase in the level of gamma-glutamyltransferase. In some patients, gamma-glutamyltransferase can reach up to 6-20 times the upper limit. Overall findings recommend that reducing the lower limit of the voriconazole trough concentration to 0.5 μg/mL can alleviate the hepatotoxicity of chronic pulmonary aspergillosis patients and maintain the clinical efficacy.

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INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a rare syndrome that is usually accompanied by mild dysfunction of the immune system followed by gradual lung tissue destruction[1]. Patients with CPA often present with pulmonary symptoms such as a persistent and/or productive cough, breathlessness, hemoptysis, weight loss, and fatigue[2]. These patients require long-term antifungal therapy to improve the symptoms and prevent the development of pulmonary fibrosis. Due to the chronicity of the disease, oral antifungal therapy is often preferred.

Voriconazole is a broad-spectrum triazole antifungal agent, which can be quickly absorbed after oral administration. The oral bioavailability of the drug can reach up to 90%-96% along with good permeability to the tissues and body fluids. In our hospital, voriconazole is often used as the first-line agent for CPA treatment. However, some patients have complained of adverse drug reactions during the treatment process, which eventually leads to discontinuation of the therapy. Common adverse reactions include hepatotoxicity, neurotoxicity, skin rash, and visual disturbances. Among these, hepatotoxicity is the most common adverse reaction. The adverse reactions of voriconazole are largely influenced by its concentration in the blood, especially the trough concentration. Reducing the trough concentration of voriconazole can reduce adverse drug reactions so that patients can eventually tolerate long-term treatment.

The cytochrome P450 2C19 (CYP2C19) polymorphism also influences the trough

concentration of voriconazole and is a significant factor contributing to the highly variable pharmacokinetics of voriconazole[3-6]. The values for plasma concentration of the CYP2C19 poor metabolizer (PM) are reportedly approximately 3 times higher than the extensive metabolizer[7]. However, there is a lack of clinically relevant studies on the relationship between CYP2C19 gene status and administration regimen.

Considering the effect of the trough concentration and CYP2C19 genetic status on the adverse drug reactions, in this study, we retrospectively analyzed 12 patients who developed hepatotoxicity during voriconazole treatment. The trough concentration was reduced by minimizing the oral voriconazole dosage. Changes in the liver function and overall treatment efficacy were recorded.

MATERIALS AND METHODS

Study design and data collection

This retrospective study included adult CPA patients admitted to Xuanwu Hospital Capital Medical University between January 2013 and January 2019. The patients' selection criteria were: (1) Positive diagnosis with CPA as per the definitions of the European society for clinical microbiology and infectious diseases and the European respiratory society[8]; (2) Patients who experienced hepatotoxicity during oral voriconazole treatment, leading to a reduced oral dose of voriconazole; and (3) Patients who continued treatment for more than 4 mo after the drug dose was reduced.

The trough concentration of voriconazole was monitored. In accordance with the requirements of the Chinese Pharmacological Society's voriconazole medication guidelines[9], the patient maintained a plasma trough concentration greater than 0.5 μg/mL after reducing the dose. During this period, a total of 21 CAP patients received voriconazole reduction therapy in our hospital. The adverse reactions mainly included hepatotoxicity in 16 patients, visual impairment in 2 patients, hallucination in 2 patients, and erythematous photosensitive rash in 1 patient. Of the 16 patients with hepatotoxicity, 3 patients with CYP2C19*1/*1 genotype showed a significant decrease in trough concentrations after the dose reduction, ranging from 0.23 to 0.48 μg/mL. All three patients were treated with other antifungal drugs instead of voriconazole. One patient with CYP2C19*1/*3 genotype could not be followed up after 1 mo of treatment. As mentioned, these patients were not included in this study. Finally, 12 patients with hepatotoxicity were included in this retrospective study.

During the same period, 25 patients with standard oral voriconazole dose (about 4 mg/kg, twice daily) and no adverse reactions served as the control group.

Demographic characteristics, underlying lung disease, CYP2C19 genotype, cereal concentration, and chest CT changes were collected on these 37 patients. The difference in treatment effect between the two groups was compared.

Therapeutic effect evaluation

Treatment response was categorized as effective, stable, or failure. The response was considered effective if there was an improvement of CPA-related symptoms, laboratory tests, and pulmonary computed tomography (CT). Patients with improved CPA-related symptoms or laboratory tests, but without any significant changes in the CT scans constituted the stable group. Patients with aggravating CT scans were part of the treatment failure group.

Statistical analyses

SPSS 19.0 statistical software was used for all statistical analyses. Categorical data were presented as frequencies and percentages. The continuous data are presented as mean and standard deviation or as median and ranges. Chi-square or Fisher's exact tests were used to compare the categorical variables. For normally distributed continuous variables, the independent samples *t*-test was used. For non-normally distributed variables the Mann-Whitney U test was applied. Statistical significance was set at 5% for all the analyses.

RESULTS

Improvement of hepatotoxicity after lowering trough concentrations of voriconazole

Before oral voriconazole treatment of CPA, 12 patients had normal liver function and no history of hepatitis. The patients were treated with a reduced dose due to hepatotoxicity within 28 to 65 d after oral administration of voriconazole (4 mg/kg). Gamma-glutamyltransferase (γ-GGT) levels were significantly elevated in all 12 patients, ranging from 213 to 996 U/L (normal range: 7-50 U/L). Four patients had alanine aminotransferase (normal range: 5-40 U/L) or aspartate aminotransferase (normal range: 8-40 U/L) more than 3 times the upper limit. The increase in alkaline phosphatase was not significant in 12 patients, with a maximum of only 153 U/L (normal range: 40-150 U/L). No patient had elevated bilirubin.

The oral dose of voriconazole was reduced to approximately 3 mg/kg in seven patients and approximately 2 mg/kg in five patients. The average trough concentrations for the 12 patients before and after voriconazole oral dose reduction were 3.17 ± 1.47 μg/mL (1.5-6.0 μg/mL) and 1.70 ± 0.78 μg/mL (0.6-3.3 μg/mL), respectively (P = 0.02). After lowering the trough concentrations, the abnormal liver function of all 12 patients was improved. Alanine aminotransferase and aspartate aminotransferase significantly improved and returned to normal levels within 1 mo. However, γ-GGT levels declined slowly. After 1 mo of drug reduction, γ-GGT levels dropped by 42.4%-75.4%, ranging from 106 to 384 U/L. After 4 mo, only three patients had γ-GGT levels returned to normal levels, and there were still five patients whose GGT level was 2 times higher than the upper limit (Figure 1).

The CYP2C19 genotypes in 12 patients were CYP2C19*1/*2 (n = 4), CYP2C19*1/*3 (n = 5), and CYP2C19*2/*2 (n = 3).

Comparison of treatment effects between two groups

Among the total 37 patients, voriconazole was indicated as the first-line treatment for CPA in 30 patients (81.1%) and second-line treatment in 7 patients (18.9%). These second-line treatment patients had previously received itraconazole therapy with a mean treatment time of 42.5 d. The mean voriconazole trough concentration of 12 patients in the reduced dose group and 25 patients in the standard dose group were 1.70 ± 0.78 μg/mL (0.6-3.3 μg/mL) and 2.22 ± 0.94 μg/mL (0.8-4.1 μg/mL), respectively. There was no significant difference in blood drug concentration between the two groups (P = 0.10). A comparison of different parameters between the two groups is shown in Table 1.

After the 4 mo treatment, in the reduced dose group, 5 of the 12 patients (41.7%) were clinically effective. In the standard dose group, 8 of the 25 patients (32%) were clinically effective after 4 mo. There was no statistically significant difference between the two groups (P = 0.72).

DISCUSSION

The treatment guidelines for CPA recommends switching to other antifungal agents such as posaconazole or itraconazole in the event of adverse drug reactions due to oral voriconazole[10]. The adverse reaction rate of itraconazole is higher (40%-50% of patients) and the symptoms include gastrointestinal upset, hair loss, peripheral neuropathy, hypertension, and ankle edema[11]. Also, due to the high price of posaconazole, it is difficult for many patients to afford it for a long time. Before giving up voriconazole treatment completely, we tried to adjust the trough concentrations of voriconazole to reduce the adverse drug reactions, so that patients can tolerate long-term drug treatment.

Recently, several independent studies have found that trough concentration is closely related to the adverse events such as hepatotoxicity, visual disturbances, and hallucinations[6,12-15]. A reduction in the voriconazole dose can lower its trough concentration and reduce or eliminate the adverse drug reactions[16]. Japanese scholars have reported that patients with hepatotoxicity have improved liver function after reducing the trough concentrations of voriconazole[17]. Our findings further corroborate these observations. All 12 patients had different levels of improvement in liver function after reducing the concentration of voriconazole.

In 12 patients, the hepatotoxicity of voriconazole mainly manifested as a significant increase in γ-GGT, higher than 200 U/L in all patients. γ-GGT is an enzyme that is present in hepatocytes and biliary epithelial cells[18]. In certain diseases, γ-GGT serum levels can be > 10 times the reference value. The guidelines of the Chinese

Table 1 Demographic characteristics and efficacy in both groups of patients

Characteristics	Reduced-dose group, *n* = 12	Standard-doses group, *n* = 25	*P* value
Demographics			
Age, median range	70.0 ± 15.8	62.8 ± 9.6	0.17
Male/female	8/4	17/8	1.00
Underlying diseases leading to CPA			
Chronic obstructive pulmonary diseases	3	9	0.71
Tuberculosis sequelae	4	1	0.03
Bronchiectasis	4	8	1.00
Lung cancer survivor	0	2	1.00
Interstitial lung disease	5	3	0.83
Steroid therapy			
Inhaled glucocorticoid	6	13	0.91
Oral glucocorticoid	7	16	1.00
Additional predisposing factors			
Diabetes	2	3	1.00
Smoking	7	15	1.00
Laboratory test after treatment			
CRP	5.1 ± 3.7	6.6 ± 5.1	0.38
ESR	24.3 ± 25.6	15.9 ± 15.0	0.31
Total immunoglobulin E	206.8 ± 269.9	279.7 ± 191.7	0.35
Trough plasma concentration	1.70 ± 0.78 μg/mL (0.6-3.3 μg/mL)	2.22 ± 0.94 μg/mL (0.8-4.1 μg/mL)	0.10
Therapeutic effect after 4 mo			
Effective	5	8	0.72
Stable + failure	5 + 2	14 + 3	

CPA: Chronic pulmonary aspergillosis; CRP: C-reaction protein; ESR: Erythrocyte sedimentation rate.

pharmacology society recommend that voriconazole be withdrawn when the patient γ-GGT level is 5 times above the upper limit[9]. However, in this study, γ-GGT levels were 6-20 times higher than the upper limit in eight patients. After reducing the lower limit of trough concentration to 0.5 μg/mL, all patients could tolerate long-term treatment, and no further deterioration of liver function was observed. This result suggests that patients without underlying liver disease can tolerate the significant increase in γ-GGT. Voriconazole reduction treatment could be tried instead of withdrawal.

The optimal trough concentration of voriconazole in patients with CPA is currently uncertain. Many studies have used a voriconazole trough plasma concentration > 1 μg/mL as the lower cut-off in patients with invasive pulmonary aspergillosis[10,19]. However, it may not be the best choice for CPA patients. Based on various *in vitro* studies, voriconazole minimum inhibitory concentrations are reportedly between 0.5 and 1 μg/mL for most of the Aspergillus species[20]. A meta-analysis involving 21 studies (including 1158 patients) demonstrated that the trough concentration of voriconazole should be maintained above 0.5 μg/mL[21]. In 2018, a practice guideline of the Chinese Pharmacological Society recommend 0.5 μg/mL as the lower limit of the voriconazole trough concentration[9]. Our retrospective study confirms that the trough concentration of voriconazole above 0.5 μg/mL could maintain good therapeutic effects. For patients with CPA who require long-term oral voriconazole therapy, maintaining a relatively safe lower trough concentration of 0.5 μg/mL may be a better option.

The CYP2C19 polymorphism influences the concentration of voriconazole. With respect to CYP2C19 extensive metabolizer, PM has a higher trough concentration of

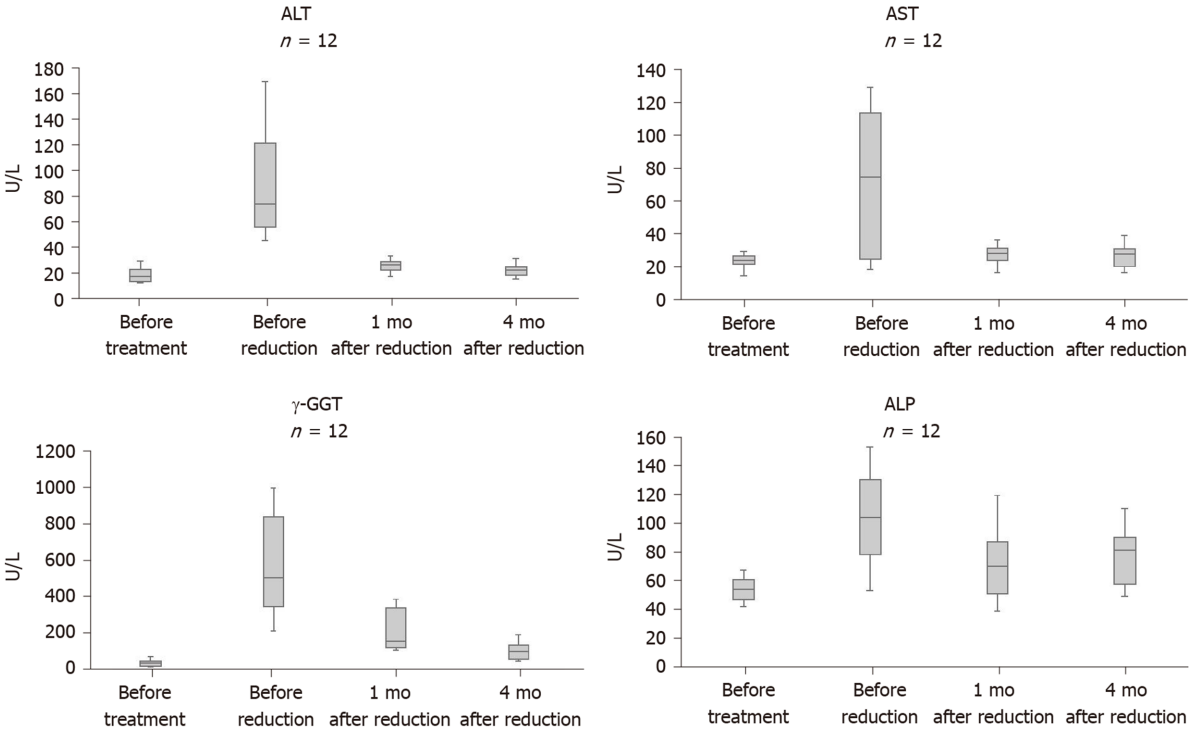

Figure 1 Changes in hepatic function tests before and after voriconazole dose reduction. Four different time points were selected: before voriconazole treatment, before voriconazole dose reduction, 1 mo after voriconazole dose reduction, and 4 mo after voriconazole dose reduction. Box plots were created to illustrate changes in alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, and alkaline phosphatase at four different time points in 12 patients with liver toxicity. Shaded regions represent the interquartile range. Capped whiskers represent the upper and lower adjacent values. Outliers are excluded. γ-GGT: Gamma-glutamyltransferase (normal range: 7-50 U/L); ALT: Alanine aminotransferase (normal range: 5-40 U/L); AST: Aspartate aminotransferase (normal range: 8-40 U/L); ALP: Alkaline phosphatase (normal range: 40-150 U/L).

voriconazole. It is proposed in the Clinical Pharmacogenetics Implementation Consortium guidelines that patients with CYP2C19 PM, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring[22]. CYP2C19 PM prevalence is 14.7% in China, which is much higher than that in European Caucasians and Africa (2.1% and 3.7%, respectively)[9]. For Chinese patients, adjusting the dose of voriconazole according to the CYP2C19 genotype may be more necessary. In our study, three patients with CYP2C19 PM (CYP2C19*2/*2) had the voriconazole dose reduced to 2 mg/kg twice daily, but the trough concentration remained 1.4-3.9 μg/mL. The results suggest that patients with CYP2C19 genotype PM could try 1/2 of the standard dose of voriconazole for treatment. However, the clinical status of all patients treated with a low trough concentration of voriconazole should be closely monitored, if the disease worsens or resistance is suspected, other antifungal agents should be considered in time.

CONCLUSION

In conclusion, reducing the lower limit of the voriconazole trough concentration to 0.5 μg/mL can alleviate the hepatotoxicity and maintained certain clinical efficacy in CPA patients. The CYP2C19 polymorphism influences the trough concentration of voriconazole, patients with CYP2C19 genotype PM could try 1/2 of the standard dose of voriconazole for treatment. However, patients should be closely monitored.

ARTICLE HIGHLIGHTS

Research background

Voriconazole is often used as the first-line agent for chronic pulmonary aspergillosis (CPA) treatment. However, some patients develop hepatotoxicity that eventually leads to discontinuation of treatment.

Research motivation

The optimal trough concentration of voriconazole in patients with CPA is currently uncertain.

Research objectives

After reducing the lower limit of trough concentration to 0.5 μg/mL, the improvement trend of liver function and therapeutic effect on the patients were recorded.

Research methods

This study retrospectively analyzed 12 adult CPA patients who developed hepatotoxicity during voriconazole treatment between January 2013 to January 2019. In these patients, the oral dose was reduced and the lower limit of voriconazole trough concentration was maintained at more than 0.5 μg/mL. Data were collected and analyzed for parameters.

Research results

Hepatotoxicity was mainly manifested as significantly increased level of gamma-glutamyltransferase in 12 patients. After lowering the trough concentrations, the hepatotoxicity was alleviated in all patients. However, gamma-glutamyltransferase levels declined slowly. After reducing the lower limit of trough concentration to 0.5 μg/mL, a certain clinical effects was still maintained.

Research conclusions

Reducing the lower limit of the voriconazole trough concentration to 0.5 μg/mL can help alleviate hepatotoxicity and maintain a certain clinical efficacy in CPA patients; however, patients should be closely monitored.

Research perspectives

This single-center retrospective study had a small sample size. Hence, additional multi-center prospective randomized study studies should be conducted to reveal the optimal trough concentration of voriconazole in CPA patients.

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