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Case Report

A Case Report of One Patient with Allergic Purpura Induced by Voriconazole

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Abstract

Voriconazole is a second-generation triazole antifungal drug, which exhibits characteristics of wide antibacterial spectrum, high biological utilization and passing through plasma brain barrier. The most common adverse reactions of voriconazole include neurological dysfunction, visual disturbance, abnormal liver function and renal dysfunction, here, this is the report to show that voriconazole can induce allergic purpura. The present report mainly describes one patient with rare adverse reactions, namely mixed type allergic purpura induced by high concentration of plasma drug caused by slow metabolism of voriconazole. After using voriconazole, the patient was diagnosed as mixed type allergic purpura, methylprednisolone sodium succinate was given for treatment. After treatment, abdominal pain and abdominal distension of the patient was significantly alleviated, and the color of rash faded. Edemas of both lower extremities were significantly improved, and the color of stool turned into yellow. The measured concentration of plasma drug of voriconazole was 15 µg/ml on admission of the patient. Genetic testing result demonstrated that the patient belonged to heterozygous mutation of CYP2C19*1*2, and the metabolism of voriconazole of the patient was relatively slow. The report prompted the clinicians that there were significant metabolic differences of voriconazole in different populations. Therefore, monitoring of drug concentration should be conducted timely in the clinical application to reduce the risk of medication and achieve individualized administration.

Keywords: Voriconazole; Allergic purpura; Adverse reaction; CYP2C19 enzyme; Individualized administration

Introduction

Voriconazole is a second-generation triazole antifungal drug, which plays antifungal role by inhibiting

cytochrome P-450 lanosterol 14 α -demethylase in the biosynthesis pathway of ergosterol. Voriconazole is used for the severe infections caused by aspergillus, fusarium and foot actinomycetes, exhibiting

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characteristics of wide antibacterial spectrum, high biological utilization and passing through plasma brain barrier. The tolerability of the drug is good, and the most common adverse reactions include neurological dysfunction, visual disturbance, abnormal liver function and renal dysfunction [1-8].

Voriconazole is metabolized mainly through hepatic cytochrome P450 isoforms CYP2C19, CYP2C9 and CYP3A4, of which CYP2C19 is the main metabolic pathway [9], but the enzyme CYP2C19 has gene polymorphism. The gene polymorphism of CYP2C19 is the main reason for the obvious individual differences of the metabolic rate of voriconazole, and studies also reveal that the genotype of CYP2C19 is closely related to the plasma concentration of voriconazole [10,11]. The adverse reactions of voriconazole are more directly associated with its concentration in plasma *in vivo* [7,12]. The metabolic differences of voriconazole in different populations are significant, of whom 15%-20% of the Asians had weak metabolism of the drug, also reminding clinicians that individualized administration should be realized in clinical application.

Case Presentation

The male patient was 55 years old. Because of discontinuous cough, chest tightness and shortness of breath in 8 years, rashes of both lower extremities for 10 days, abdominal pain, abdominal distension, and rashes of the right hand and right forearm for 5 days, he was admitted to our hospital. The patient had cough and expectoration without obvious inducement 8 years ago. The color of phlegm was yellow and white, and the quantity was more, which could not be coughed out easily. The cough was accompanied by chest tightness and shortness of breath, which was aggravated after movements. The patient had visited the local hospital and he was diagnosed as "Chronic obstructive pulmonary emphysema". The patient got better after being given anti-infection, reduced phlegm and asthma treatment. The patient was hospitalized for treatment in our hospital because of cough aggravating for 1 month. According to the result of sputum culture after admission to our hospital, he was given Cefoperazone Shubatan for anti-inflammation, and he was treated with Micafungin for antifungal therapy, and sequentially

Piperacillin tazobactam sodium and Voriconazole for anti-inflammatory treatment. Breathing of the patient was improved, and cough and expectoration was alleviated, and the disease condition was improved. The antiasthmatic and antitussive drugs were taken continuously after discharge, and voriconazole tablets were taken orally with 200 mg q12 hours (h). On the seventh day after taking voriconazole tablets, the patient had rashes of both lower extremities, anomalous, perceived blurred vision and change of color sense, which were improved after lasting for 20 minutes. On the ninth day after using the drug, there was visible multiple dotted and schistose purpura hemorrhagica on the double lower calves and edemas of the patient (Figure 1), and there were rashes on the right hand and the right forearm, abdominal pain, abdominal distension, stool frequency, melena and bilateral knee pain. On the tenth day after using the drug, the patient stopped taking voriconazole tablets by himself and he was admitted to our hospital for diagnosis and treatment. Admission for physical examination: the whole abdomen was soft, and there was upper abdominal tenderness. No deformity was in the extremities, and multiple scattered red rashes were seen in the right forearm and right hand. The borders of rashes were clear, and the color did not fade when pressing. The hands had edemas. There was visible multiple dotted and schistose purpura hemorrhagica on the double lower calves, the color of which did not fade when pressing. The skin of both lower extremities was dry, and there was concave edema without subcutaneous nodules or lumps. Swelling of bilateral ankle joints, tenderness, and tenderness of the double knee joints. The examination results of the routine blood test at the time of admission showing the following aspects: WBC $14.97 \times 10^9/L$, N 79.2%, Hb 109 g/L, PLT $328 \times 10^9/L$; Positive feces occult plasma; urine routine: occult blood 3+, glucose 3+, red blood cell 44.8/HPF, positive pathological tube type, white blood cell 141.62/HPF; nine items in emergency treatment: potassium 4.9 mmol/L, sodium 134 mmol/L, urea 11.16 mmol/L, creatinine 99 $\mu\text{mol/L}$, glucose 13.35 mmol/L. The liver and kidney function examination results in 6 days after admission: creatinine 166 $\mu\text{mol/L}$, urea 24.05 mmol/L, albumin 21.2g/L, globulin 32.8g/L, glucose 7.55 mmol/L; fecal routine result: occult blood trace. Urine routine results: occult blood 2+, protein 2+, red blood cell 16.4/HPF. On admission, the diagnosis was

Figure 1: The visible multiple dotted and schistose purpura hemorrhagica on the double lower calves of the patient.

as follows: 1. chronic obstructive pulmonary disease type II respiratory failure, chronic pulmonary heart disease 2. Double-lung disease 3. Type 2 diabetes.

The edemas of both lower extremities and the rashes of the right hand and the right upper arm were significantly improved and the color of stool turned yellow on the fourth day (i.e., the third day after admission) when the patient stopped taking drugs. According to the typical clinical symptoms of the patient such as multiple dotted and schistose purpura hemorrhagica on the double lower calves, abdominal pain, abdominal distension, hemorrhage of digestive tract and damage of renal function by the clinicians on the fifth day after stopping drugs, the diagnosis of allergic purpura was added, and the patient was intravenously dripped with 40 mg qd methylprednisolone sodium succinate. After symptomatic treatment by giving acid suppression, protection of gastric mucosa and relieving pain, the abdominal pain and abdominal distention of the patient was relieved, and the color of rashes faded significantly and the edemas of both lower extremities were alleviated. The examination results of the functions of liver and kidney at the time of discharge were as follows: creatinine 76 $\mu\text{mol/L}$, urea 20.09 mmol/L, albumin 21.2 g/L, globulin 32.8 g/L, glucose

7.55 mmol/L; the fecal routine results: negative occult blood; urine routine: occult blood 1+, protein 1+, red blood cell 7.5/HPF, indicating that the renal function of the patient was improved. The gene detection results of the patient illustrated that he belonged to the CYP2C19*1*2 heterozygous mutation. The metabolism of voriconazole of the patient was slow, and the plasma drug concentration of voriconazole measured on admission was 15 $\mu\text{g/ml}$, significantly higher than that of the normal value.

Discussion

The probability of occurrence of adverse reactions of voriconazole is closely related to the plasma drug concentration of the drug *in vivo* [7,12]. The target plasma concentration range of voriconazole is 1.0-4.0 $\mu\text{g/ml}$ currently, and the probability of occurrence of adverse reactions will be significantly increased when the level of voriconazole is higher than 4.0 $\mu\text{g/ml}$. The study of Suzuki Y discovered that the risk of liver toxicity increased significantly when the plasma concentration of voriconazole was relatively high *in vivo* [12]. The main reason of the distinct plasma drug concentrations of voriconazole in different patients given the same dose of voriconazole was that the metabolisms of

voriconazole in distinct patients are different. The effect of hepatic drug enzyme on the metabolism of voriconazole is the largest, and the activity, quantity and distribution of the hepatic drug enzyme is related to heredity. In other words, genetic polymorphisms affect drug metabolism and the interactions between drugs, thereby affecting the efficacy and leading to adverse reactions. So-called genetic polymorphism refers to the occurrence of genetic variations caused by one or more allele mutation. An important source of the racial and individual differences in drug metabolism is associated with genetic polymorphism. Voriconazole is metabolized mainly through hepatic cytochrome P450 isoforms CYP2C19, CYP2C9 and CYP3A4, of which CYP2C19 is the main metabolic pathway, but the enzyme CYP2C19 has gene polymorphism. Generally, it is divided into four phenotypes: fast metabolic type of the individual with normal enzyme activity, slow metabolic type of the individual without enzyme activity, intermediate metabolic type of the individual decreased enzyme activity and super metabolic type of the individual with significantly increased enzyme activity. The gene polymorphism of CYP is the main reason for the obvious difference of the metabolism rate of drugs. The study also confirmed that the genotype of CYP2C19 was closely related to the plasma concentration of voriconazole [10,11]. The gene detection revealed that the patient of the present report belonged to the heterozygous mutation of CYP2C19*1*2, indicating that the enzyme of CYP2C19 of the patient belonged to the intermediate metabolic type. The metabolic ability of this type of enzyme on voriconazole is average, and the plasma concentration of voriconazole of this type of patient is 3 times higher than that of the fast metabolism patient, and the patient of the present report is prone to adverse reactions. The measured plasma concentration of voriconazole of the patient when the patient was admitted to hospital was 15 µg/ml, and the result also confirmed that the metabolic rate of the patient of the genotype on voriconazole was low, so the plasma drug concentration was higher. Therefore, it is demonstrated by the gene detection and the detection results of plasma drug concentration that the adverse reactions of Allergic Purpura of the patient were mainly related to the slow metabolism of voriconazole, leading to the accumulation of voriconazole in the body of the patient.

Allergic purpura is a common vascular allergic reaction disease. Allergic reactions are produced by some sensitization substances in bodies, leading to increased capillary fragility and permeability, extravasation of plasma, resulting in purpura, and haemorrhage of mucosa and some organs. In addition to purpura, the clinical features include abdominal pain, nephritis and arthritis symptoms. The clinical symptoms are classified as simple type, abdominal type, joint type, renal type and mixed type. The patient had rashes of extremities and multiple dotted and schistose purpura hemorrhagica on the double lower calves combined with abdominal pain and abdominal distension syndromes and renal damage, which was diagnosed as the mixed type of Allergic Purpura and the diagnosis was clear. In addition to voriconazole in the medical record according to the personal statement of the patient, the patient has been taking antiasthmatic, antitussive and anti-inflammatory and antidiabetic drugs recently, and there was no changes of drugs except for oral taking of voriconazole only before and after the last discharge when above symptom appeared. Therefore, it can be basically determined that the adverse reactions of the patient is mainly allergic purpura induced by drugs, which has no relation with the progression of the original disease. In addition, on the seventh day after taking voriconazole Tablets, the patient had rashes of both lower extremities, anomolopia, perceived blurred vision and change of colour sense, which were improved after lasting for 20 minutes. The appeared anomolopia, perceived blurred vision and change of colour sense are the common adverse reactions of voriconazole, which is consistent with the reported literatures and it generally can be recovered. On the ninth day after using the drug, there was visible multiple dotted and schistose purpura hemorrhagica on the double lower calves and edema of the patient, and there were rashes on the right hand and the right forearm, abdominal pain, abdominal distension, stool frequency, melena and bilateral knee joint pain. After stopping of using drugs, the edemas of both lower extremities and rashes of the right hand and the right upper arm of the patient were significantly improved and the color of stool turned into yellow, all of which indicate the appeared allergic purpura of the patient and taking voriconazole have corresponding time relationship.

The above clinical data indicate that the clinicians all should conduct correct education for the patients in the future work whether taking voriconazole in hospital or outside the hospital, and the clinicians should inform the patients the adverse reactions that might be caused and timely give medical treatment and adjust dose of drugs or replace treatment drugs. Before using voriconazole, the detailed allergic histories of the patients should be asked, and the drug should be used with caution for the patients with allergic history and allergic persons. In addition, the metabolic differences of voriconazole in different populations are significant, and the drug of voriconazole should be used in combination with the genotypes of patients, and monitoring of drug concentration should be conducted timely to reduce the risk of medication and achieve individualized administration. In the course of the drug use, the indication and usage and dosage specified in the instructions should be followed strictly, and the compatibility taboo and the combined medication should be paid attention to avoid adverse drug reaction/adverse drug event (ADR/ADE) induced by the interaction of drugs.

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