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Voriconazole-Related Myopathy in a Liver Failure Patient: A Case Report

Case Report

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Abstract

Voriconazole (VRC) is a broad-spectrum triazole antifungal drug and first-line choice for invasive pulmonary aspergillus (IPA) even in patients with liver failure. But it is limited when used in these individuals due to hepatoxicity and supratherapeutic trough plasma concentrations that could lead to severe adverse events appear or aggravate.

This case reported a 41-year-old Chinese male who suffered from sub-acute liver failure and received VRC for treatment of IPA. Fifteen days later, the patient developed a rare side effect, myopathy, manifested by a sharp increase in muscle enzymes accompanied with severe fatigue. The drug was stopped then because the concentration was supratherapeutic. After that, his symptoms relieved and creatine kinase level decreased to normal range.

To prevent adverse events of VRC in patients with liver deficiency, routine therapeutic drug monitoring (TDM), and dosage adjustment are recommended. In addition, monitoring side effects of the drug is significant as well.

Keywords

Voriconazole; Myopathy; Liver failure; Adverse event

Abbreviations

VRC: Voriconazole; IPA: invasive pulmonary aspergillus; TDM: Toutine Therapeutic Drug Monitoring; NR: Normal Range; ALT: Alanine Transaminase; AST: Aspartase Transaminase; TBiL: Total Bilirubin; INR: International Normalized Ratio; WBC: White Blood Cell; CT: Computed Tomography; Sck: Serum Creatine Kinase; CK-MB: Creatine Kinase Isoenzyme MB

Introduction

Patients with liver failure are commonly associated with variable and non-uniform reductions in drug-metabolizing activities, leading to its accumulation and hazardous plasma concentrations [1]. They are immunocompromised and at high risk of invasive aspergillus infection [2]. Generally, empirical and preemptive antifungal therapy such as voriconazole (VRC) should be initiated immediately when invasive pulmonary fungal infections are suspected in these individuals [3].

Voriconazole is a broad-spectrum azole antifungal and is a first-line agent for the treatment of invasive aspergillosis. It is extensively metabolized by hepatic cytochrome

P450 (CYP) enzymes, principally by CYP2C19 and, to a lesser extent, by CYP3A4 and CYP2C9. The plasma trough concentration of 1-5.5 μg/mL for VRC is recommended [2,4]. Narrow therapeutic window, nonlinear pharmacokinetics coupled with genetic polymorphisms in the CYP2C19 gene account for high interpersonal variability in clinical response. Therefore, routine therapeutic drug monitoring (TDM) for plasma levels is recommended between 2-5 days after initiation of therapy, and repeated monitoring is necessary until steady state level is in the therapeutic range [2].

Most patients show well tolerance for VRC. Commonly reported adverse events are hepatotoxicity, neurotoxicity (visual hallucinations, encephalopathy, neuropathy), photopsia, skin rash, photosensitivity and visual disturbance which have been validated correlated with the drug's trough concentration and may warrant discontinuation of therapy [5,6]. Cutaneous malignancies, arrhythmias, alopecia, nail changes, and electrolyte abnormalities are unusual adverse effects that have been reported recently [7]. Myopathy has seldomly been reported with voriconazole. There are only two such cases has been described in the literature, one for post lung transplant patient and the other for post renal transplant patient [8,9]. However, the concentration has not been monitored dynamically in the two cases, so none of them can reflect the correlation between VRC concentration and myopathy.

Here we report a rare case of VRC-related myopathy with progressing fatigue and elevated muscle enzymes that relieved upon drug discontinuation in a middle-aged male patient with liver failure.

Case Report

A 41-year-old Chinese male, presented with subacute liver failure caused suspected by viral infection, was admitted on Nov 26th, 2014, with progressively worsened jaundice for 7 days and systemic fatigue and gastrointestinal symptoms for 10 days. He denied history of liver disease, alcohol, drug abuse, heart disease, skeletal muscle myopathy, trauma, hypothyroidism, convulsion, central nervous system disease, malignant hyperthermia and malignant tumor.

Laboratory tests at admission are as follows: alanine aminotransferase (ALT), 652.1U/L (NR 0-40U/L); aspartate aminotransferase (AST), 297.8U/L (NR 8-40U/L); total bilirubin (TBil), 396.3μmol/L (NR 3.4-17.1μmol/L);alkaline phosphatase (AKP), 147.1 IU/L (NR 39-117IU/L);international normalized ratio (INR), 2.36 (NR 0.85-1.20); prothrombin time activity (PTA), 34.5% (NR 80%-120%); serum copper and ceruloplasmin levels were within NR. Routine blood tests were normal. Serum markers for hepatitis A, B, C, and E, anti-EBV IgM, anti-CMV IgM, anti-HIV IgM, and autoantibodies were negative. He was diagnosed with subacute liver failure of unknown etiology.

After admission, liver function gradually deteriorated (Figure 1), even appeared grade 2-4 hepatic encephalopathy between December 3-5. Then, latamoxef was applied for antimicrobial prophylaxis and stopped on Dec 12th. Unfortunately, he developed fever and hyperpyrexia with raised WBC count ($11.11*10^9$/L, NR $3.5-9.5*10^9$/L) and neutrophil percentage (82.1%, NR 50-70%)on Dec 21th, without apparent respiratory symptoms. Meanwhile, the TBil raised obviously and was thought related to infection. Therefore, we suspected he had a bacterial infection and initiated treatment with intravenous latamoxef (1g every 8h), but it wasn't effective with remain febrile after 48 hours therapy and substituted for meropenem on Dec 23th. His model for end-stage of liver disease (MELD) score was 27.Sputum culture and serum galactomannan (GM) test were negative. (1-3)-β-D-glucan level was 62.5pg/mL (NR 0-60pg/mL). Subsequently, thoracic CT imaging (Figure 2A) revealed bilateral pulmonary high-density shadow and we suspected he suffered from possible invasive aspergillosis [10]. As a result, we administered preemptive antifungal treatment with VRC (400mg every 12h for 2 doses followed by 200mg every 12h) intravenously on Dec 24th. Cefoperazone sulbactam was added to replace meropenem on Dec 30thfor de-escalation antibiotic therapy. The patient tolerated the treatment and responded well, liver function was significantly improved by day 13 of the treatment, with TBil and INR dropped (Figure 1). Clinical manifestations and CT imaging on Jan 5th (Figure 2B) also suggested that the infection was well controlled. Butserum potassium of 2.9mmol/L was detected on the 14th day. By intravenous replacement with potassium chloride and oral supplements, serum potassium was increased to normal within one day. Unfortunately, the patient felt obvious fatigue and found it difficult to raise his head on 15 days after VRC taking, without underlying heart disease, chest discomfort, changes in muscular tension of limbs and neurological abnormalities. Consequently, we tested the muscle enzymes, which were apparently abnormal. The

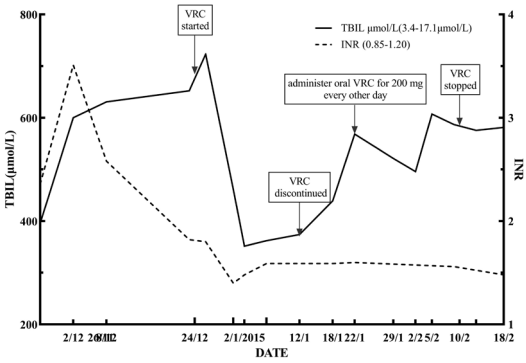

Figure 1: The dynamic changes of liver function tests

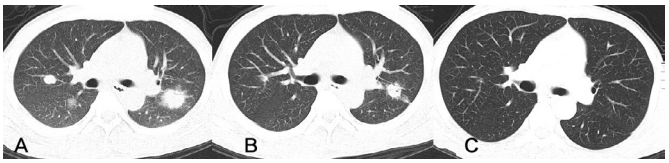

Figure 2: Thoracic CT scan at baseline (A), 13 days (B) and 2 months (C) after treatment, indicating high density shadow had shrunk and vanished finally.

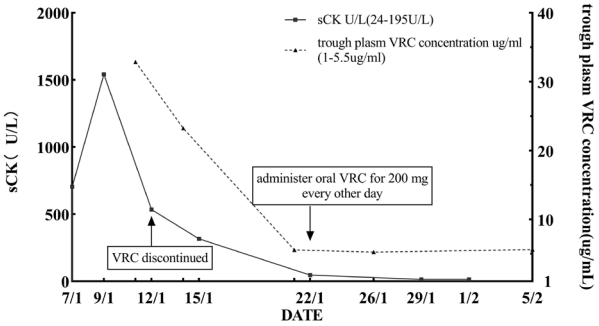

Figure 3: Dynamic changes of sCK level and trough plasm concentration during VRC treatment

sCK value was 705.5U/L (NR 24-195U/L), CK-MB was 25.3U/L (NR 0-24U/L), MYO was 4089.6μg/L (NR 20-70μg/L), potassium level was 3.42mmol/L. Troponin was within the normal range. The cardiac biomarkers and electrolyte were monitored continuously (Figure 3). Due to the elevation of sCK and MYO were more remarkable than CK-MB, with CK-MB/sCK <0.06 and troponin levels in normal range, we considered acute muscle injury rather than cardiac factors.

There are none reports about meropenem, latamoxef, and cefoperazone sulbactam related myositis and electrolyte disturbances. Thus, we tested the serum VRC concentration on the 20th day which was much higher than the therapeutic range (32.86μg/mL) and we had to stop it.

Eleven days past, the plasma VRC concentration dropped to 5.57μg/mL. The level of CK, CK-MB and MYO decreased to normal and the symptoms were gradually relieved. These symptoms were thought to be caused by high plasma concentration of VRC. Because the pneumonia hasn't been healed, we began to administer oral VRC for 200 mg every other day on January 22th. The concentration was in normal range (5.27 ug/mL). Seven days later, the serum potassium was dropped to 3.0mmol/L again.

A follow-up CT scan performed on February 26 revealed that the high-density shadow had diminished (Figure 2C). The patient was discharged on April 11th, 2015. After discharging, we tested his CYP2C19 phenotype which is intermediate metabolizer (CYP2C19*1*3). Follow-up results showed stable liver function and liver biopsy indicated severe chronic hepatitis, G3+/S4-.

Discussion

Our patient was a case of subacute hepatic failure without previous history of cardiovascular, renal or neurological disease. He received standard dose of voriconazole intravenously for possible IPA. The antifungal treatment was effective with liver function improved.

Furthermore, the patient suffered from myopathy during VRC treatment without complaints of neck muscle before administration and other causes of myopathy .The VRC plasma concentration was far beyond therapeutic range, while the cardiac biomarkers elevated. And the myocardial enzymes levels were decreased after discontinued VRC treatment. Accordingly, we concluded the myositis was likely associated with VRC [11].

Elevated creatase and clinical manifestations recovered spontaneously after VRC discontinuation, suggesting that they are reversible and should be detected earlier to reduce the occurrence of drug-related myopathy and minimize the influence on therapy.

Besides, when were-administrated VRC at a reducing dose, the concentration and serum creatinase were within a safety range, indicated that the myopathy alluded to earlier might be a kind of concentration dependence side effect.

The patient developed hypokalemia twice during treatment, with normal kidney function and no history of administering potassium drugs such as furosemide. Hypokalemia is reported as a very rare side effect of VRC [12]. Therefore, the possible causes of hypokalemia might be the application of VRC and insufficient potassium intake. Severe hypokalemia, defined as serum potassium below 2.5mmol/L, can cause fatigue, muscle weakness, and eventually rhabdomyolysis which is always accompany with sCK levels well above 5 times the normal limit and plasma myoglobin increases rapidly [13]. There are no reports of rhabdomyolysis caused by moderate hypokalemia, so we exclude hypokalemia caused rhabdomyolysis and the association between hypokalemia and fatigue.

Fatigue is one of the common symptoms of liver failure, which is easy to be ignored. For these patients, using VRC usually may aggravate the symptom and weaken them. Therefore, it's essential to look out for drug-induced myopathy caused by overdose of VRC in liver dysfunction patients.

VRC pharmacokinetics may be affected by patients' polymorphism in CYP2C19 genotype, age, race, liver function, and concomitant medications, including clopidogrel, proton pump inhibitors, and diazepam [14]. Intermediate metabolizer CYP2C19 genotype and deteriorated liver condition of the patient might have contributed to supratherapeutic VRC concentration.

Wang et al found that none of patients with Child-Pugh score C had a trough concentration lower than 1μg/mL, and it is higher than 5.0μg/mL in most cases [3]. One study reported that a VRC levels >3.0mg/L is associated with increased hepatotoxicity [15]. Moreover, VRC related hepatoxicity might aggravate liver failure further. Therefore, dosage adjustment for these individuals has been proposed. The instruction recommends to halve the VRC maintenance dose in cirrhotic patients with Child-Pugh score A or B. In addition, a Japanese study indicated that cut the oral maintenance dose to approximately one-third in patients with Child-Pugh C liver cirrhosis would prevent adverse drug reactions and increase the efficacy of VRC [16]. However, there are rare researches on its safety in patients with severe liver dysfunction, non-cirrhotic liver failure or post-liver transplantation. Therefore, it is necessary to establish the VRC recommended dosage model for these individuals.

Conclusions

In conclusion, we suggest the dosage adjustment or individualized medication of VRC should be conducted in patients with liver dysfunction. Moreover, conducting TDM earlier and more frequent and liver function monitoring in liver failure patients is necessary. Before VRC administered, electrolyte and myocardial enzymes should be tested. Qualified patients can even be tested for CYP2C19 genotype. For patients with liver failure and poor metabolizer CYP2C19 genotype, echinocandins antifungal drug [17,18], and liposome amphotericin B are recommended[19]. Our case has several limitations. First, GM test had only be detected once in serum before antifungal therapy. And bronchoalveolar lavage (BAL) fluid wasn't got. Second, the antimicrobial prophylaxis in liver failure was not necessary according toa retrospective cohort study [20].

Declarations

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Contributors lists

M. J collected data, and drafted the manuscript; S.W and M.Y contributed to the revision of the manuscript; M.Z performed data interpretation, and revised critically the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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