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CASE REPORT

Drug Analysis of Voriconazole Combined with Granulocyte Colony Stimulating Factor

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SUMMARY

Background: **The aim of the study was to improve the clinical cognition of leukemia-like reaction caused by voriconazole and granulocyte colony-stimulating factor and to avoid misdiagnosis or delayed diagnosis.**
Methods: **A case of drug analysis of Voriconazole combined with granulocyte colony stimulating factor was retrospectively analyzed and related literature was reviewed.**
Results: **Blood routine of the patient on July 29: WBC 13.48 x 10^9/L, neutrophil 85.3%, lymphocyte 13.4%, hemoglobin 111 g/L, platelet 285 x 10^9/L. Vancomycin was given to prevent intracranial infection. Lumbar puncture was performed on July 30, cerebrospinal fluid was sent for routine and biochemical examination, leukocytes were 0.15 x 10^9/L, monocytes 45%, polynuclear cells 55%, protein 1.172 g/L, Acinetobacter baumannii and Candida clorbicus were detected in sputum culture, vancomycin and meropenem static sites were given to prevent intracranial secondary infection. Fungi were detected in urine culture, and voriconazole was given to prevent fungal infection. Blood routine: White blood cell 0.61 x 10^9/L, neutrophil 23%, lymphocyte 73.8%, red blood cell 2.65 x 10^{12}/L, hemoglobin 77 g/L, platelet 17 x 10^9/L, bone marrow was extracted after medication. Bone marrow images show poor myelodysplasia, with granulocytes dominated by proto-early cells. Subsequent flow cytometry, chromosomal karyotype, and fusion gene analysis were performed to exclude the possibility of leukemia. Flow cytometry showed that the proportion of myeloid primordial cells was not high, the granulocytes were mainly at the early and young stage, no abnormal phenotype was observed in erythrocytes, monocytes and NK cells, no obvious mature B lymphocytes were observed, and the ratio of $CD4^+/CD8^+$ was decreased. Karyotype results showed that there was no mitotic phase. The results of fusion gene analysis showed that the fusion gene was negative or lower than the detection sensitivity. Voliconazole was stopped first, and granulocyte colony stimulating factor was stopped 3 days later. Two weeks later, blood and bone marrow images basically recovered, white blood cell 7.88 x 10^9/L, neutrophil 46.3%, lymphocyte 48.2%, hemoglobin 126 g/L, platelet 142 x 10^9/L, bone marrow hyperplasia active. The proportion of three series is roughly normal.**
Conclusions: **The reason for the occurrence of leukemia-like reaction in this patient was considered to be related to voriconazole and granulocyte colony stimulating factor, cessation of voriconazole and granulocyte colony stimulating factor, and recovery of blood and bone marrow images. In the clinical use of voriconazole and granulocyte colony stimulating factor, close attention should be paid to the drug interaction and individualized medication should be carried out to ensure the safety of medication.**
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KEYWORDS

leukemia-like reaction, voriconazole, granulocyte, granulocyte colony stimulating factor, pancytopenia, severe infection

INTRODUCTION

Drug interaction refers to the compound effect produced in patients taking two or more drugs at the same time or within a certain period of time, which can enhance the efficacy or reduce side effects, or weaken the efficacy or cause unnecessary toxic and side effects [1]. Voriconazole is a triazole antifungal drug, which is a broad-spectrum antifungal drug. The demethylation of 14α-sterol mediated by cytoplasmic P450 inhibits biosynthesis of ergosterol and plays an antifungal role. It has bactericidal effects on Candida, Aspergillus and other fungi, and is a first-line drug for the treatment of severe aspergillus infection [2,3]. Common adverse reactions of voriconazole include abnormal liver function, rash, and visual impairment, etc. [4]. Granulocyte colony stimulating factor is mainly used in the prevention and treatment of leukopenia caused by tumor radiotherapy or chemotherapy, the treatment of bone marrow hematopoietic dysfunction and myelodysplastic syndrome, the prevention of potential infection complications of leukopenia, and the acceleration of recovery of neutropenia caused by infection. Common adverse reactions of granulocyte colony stimulating factor include abnormal liver function, bone pain, lumbago, arthralgia, rash, nausea, vomiting, etc. The adverse effects of voriconazole combined with granulocyte colony stimulating factor inducing leukemia like reactions have not been reported. The purpose of this study was to report a case of leukemia like reaction after voriconazole and granulocyte colony stimulating factor administration. Clinical pharmacists made timely judgment and provided suggestions for adjustment of medication regimen, providing reference and basis for rational clinical use of voriconazole and granulocyte colony stimulating factor.

CASE REPORT

The patient, male, 41 years old, was admitted to the emergency room of Handan Central Hospital on July 23, due to "brain contusion and laceration caused by high fall". After that, he was transferred to the second Ward of the Neurosurgery Department and immediately underwent brain surgery. His condition was stable after surgery, and he was given mannitol to relieve intracranial edema and nutritional nerve and other supportive treatments. Blood routine of the patient on July 29: WBC 13.48 x 10^9/L, neutrophil 85.3%, lymphocyte 13.4%, hemoglobin 111 g/L, platelet 285 x 10^9/L. Vancomycin was given to prevent intracranial infection. Lumbar puncture was performed on July 30, cerebrospinal fluid was sent for routine and biochemical examination, leukocytes were 0.15 x 10^9/L, monocytes 45%, polynuclear cells 55%, protein 1.172 g/L, Acinetobacter baumannii and Candida clorbicus were detected in sputum culture, vancomycin and meropenem static sites were given to prevent intracranial secondary infection. On August 20, the patient had abdominal distension, and was given gastrointestinal decompression. Fungi were detected in urine culture, and voriconazole was given to prevent fungal infection. Blood routine: White blood cell 0.61 x 10^9/L, neutrophil 23%, lymphocyte 73.8%, red blood cell 2.65 x 10^{12}/L, hemoglobin 77 g/L, platelet 17 x 10^9/L, intravenous infusion of dexamethasone and subcutaneous injection of granulocyte colony stimulating factor and thrombopoietin, bone marrow was extracted after medication. Bone marrow images show poor myelodysplasia, with granulocytes dominated by proto-early cells (Figure 1 and 2). Diagnosis was difficult. Subsequent flow cytometry, chromosomal karyotype, and fusion gene analysis were performed to exclude the possibility of leukemia. Flow cytometry showed that the proportion of myeloid primordial cells was not high, the granulocytes were mainly at the early and young stage, no abnormal phenotype was observed in erythrocytes, monocytes, and NK cells, no obvious mature B lymphocytes were observed, and the ratio of $CD4^+/CD8^+$ was decreased. Karyotype results showed that there was no mitotic phase. The results of fusion gene analysis showed that the fusion gene was negative or lower than the detection sensitivity. It is suspected to be a leukemia-like reaction induced by granulocytopenia after static site voriconazole followed by granulocyte colony stimulating factor. Voliconazole was stopped first, and granulocyte colony stimulating factor was stopped 3 days later. Two weeks later, blood and bone marrow images basically recovered, white blood cell 7.88 x 10^9/L, neutrophil 46.3%, lymphocyte 48.2%, hemoglobin 126 g/L, platelet 142 x 10^9/L, bone marrow hyperplasia active. The proportion of three series is roughly normal. Follow-up treatment and follow-up of primary disease: The patient will be discharged at the end of November when his consciousness improves. The patient was followed up for more than 6 months, and there were no pathological changes in clinical and laboratory examinations.

DISCUSSION

The differential diagnosis of granulocytopenia includes viral infection, chemical effects, hematologic diseases, and rare familial diseases. Through clinical cases, we found that patients with hepatitis A, hepatitis B, hepatitis C, syphilis, and AIDS were negative. No history of blood diseases or rare family diseases. This suggests drug-induced granulocytopenia. The pathogenesis of drug-induced granulocytopenia is as follows: 1) Immune-mediated hypersensitivity unrelated to drug dose; 2) caused by drug poisoning: the performance is related

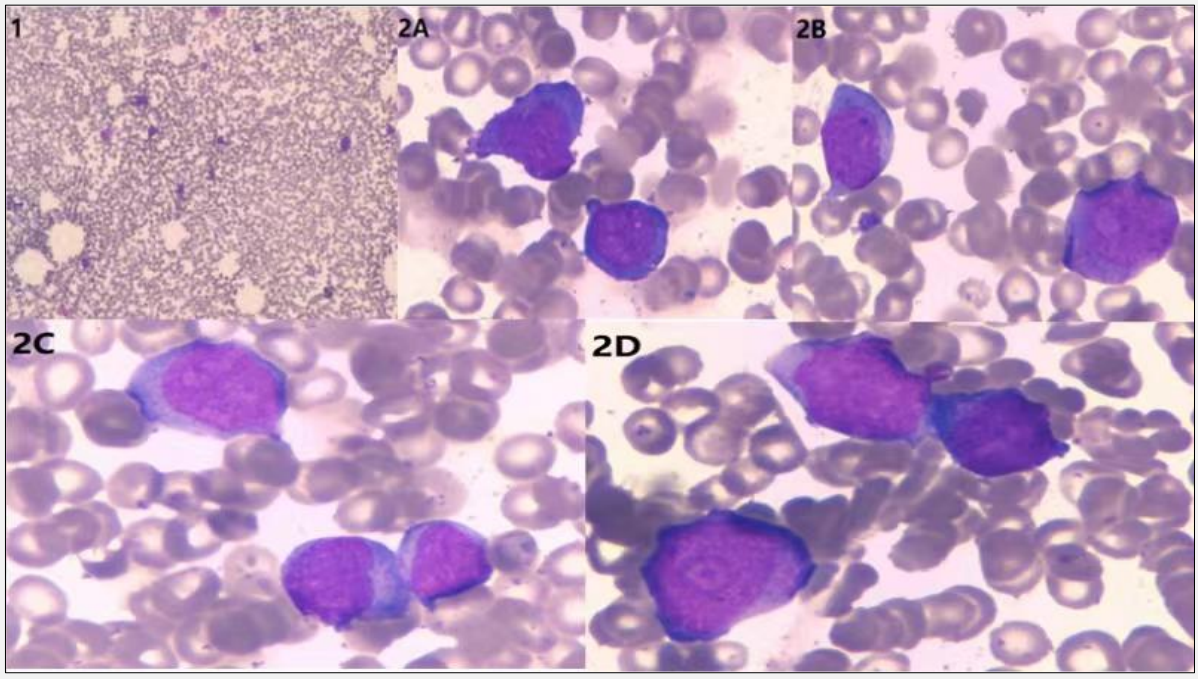

Figure 1. Bone marrow image showing pancytopenia with numerous abnormal cells (Giamsa stain 10* 10).
Figure 2 (A - D). This bone marrow image shows proto-early granulocyte cells (Giamsa stain 10* 100).

to the drug dose. In this case, the patient's granulocytopenia was due to voriconazole, which did not cause granulocytopenia due to its resting point of mannitol, vancomycin, and meropenem for nearly a month, so it is unlikely that they caused it. In clinical studies, there is no correlation between the minimum inhibitory concentration of voriconazole and clinical efficacy, and there seems to be no correlation between the blood concentration of voriconazole and clinical efficacy [5]. Therefore, the underlying mechanism of voriconazole's adverse reactions remains unclear. Patients with granulocytopenia were treated with granulocytopenia colony stimulating factor, and the two drugs interacted to produce myelosuppression. Drug interactions can be classified as pharmacokinetic and/or pharmacodynamic interactions depending on how they occur. Pharmacokinetic interactions are mainly caused by drug interactions in absorption, distribution, metabolism, and excretion, and metabolic drug interactions have the highest incidence. Some studies have reported that about 90% of clinical metabolic drug interactions are caused by changes in P450 enzyme activity [6]. Voriconazole's antifungal effect is caused by cytochrome P450-mediated demethylation of 14α-sterol, thereby inhibiting ergosterol biosynthesis [7]. Therefore, we have reason to suspect that the combination of voriconazole and granulocyte-colony-stimulating factor may be responsible for a leukemic response following metabolic drug interactions. Drug-induced leukemia-like reactions may be reversible, and early identification, treatment, and rapid control of the disease may prevent further deterioration. In this case, the clinician changed the anti-infection regimen in time to avoid serious consequences. Because voriconazole pharmacokinetics are easily affected by many factors, in clinical use of voriconazole, clinicians should monitor its normal blood drug concentration, conditional drugs for patients should have genetic testing, close attention should be paid to drug interactions, and it is beneficial to develop an individualized dosage regimen to improve efficacy, and reduce adverse reactions and to ensure drug safety [8,9].

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Declaration of Interest:
All authors declare: 1. All views and data in this paper are supported by references and data. The manuscript has not been published before and is not being considered for publication elsewhere. 2. All authors have contributed to the creation of this manuscript for important intellectual content and read and approved the final

manuscript. We declare there is no conflict of interest. 3. This paper is published with the consent of patients, in line with ethical requirements.

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