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CASE REPORT

Amphotericin B May Decrease the Serum Level of Voriconazole: A Case Report and Brief Review of Literature

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Background: Combination therapy with amphotericin B (AmB) and Voriconazole are sometimes used due to reducing AmB-related adverse reactions and improving outcomes. However, there was no report whether AmB would affect the serum level of Voriconazole.
Case Presentation: A patient was in presumption of invasive fungal infection. Voriconazole and amphotericin B was combined for administration. The results showed that serum levels of Voriconazole were dramatically reduced when combined AmB, whereas went up when receiving Voriconazole alone.
Conclusion: AmB might decrease the level of Voriconazole. Such a combination of AmB and Voriconazole cannot be considered appropriate until more data are available.
Keywords: amphotericin B, voriconazole, fungal infection, drug interaction

Background

Amphotericin B (AmB) is a broad-spectrum antifungal agent produced by the bacterium Streptomyces nodosus. It is indicated for the treatment of life-threatening invasive fungal infection. However, adverse events, particularly nephrotoxicity, are limiting factors in achieving an effective dose. In order to reduce adverse reactions and improve outcomes, combination antifungal therapy is sometimes administrated. This will inevitably enhance the risk of clinically significant drug–drug interactions. In review of the literature, about 8 cases reported the therapeutic efficacy of AmB in combination with Voriconazole in invasion fungal infection.[1–8] However, there is no literature on the two drug interaction. Here, we present a case of drug interaction between AmB and Voriconazole, which has not been described in the literature.

Case Presentation

A 57-year-old man was admitted to our hospital in August 2020 on account of significant loss of weight and appetite over the past 4 months and fever for 1 month. Few positive findings were noted on the physical examination except the patient was poor development with a body weight of 45 kg (body mass index: 14.2 kg/m^2), and had anemic appearance and hepato-splenomegaly. No palpable lymph nodes were found. The patient was HIV-seronegative and was considered immunocompetent. He was a builder. On admission, the serum 1.3- beta-D-glucan level increased significantly. The *Histoplasma capsulatum* was presumed by microscopic examination of the bone marrow smear (Figure 1). However, no measurement was made for *Histoplasma capsulatum* antigen. Drug susceptibility testing for *Histoplasma capsulatum* should have been performed, but unfortunately, we did not conduct it since the blood and bone marrow culture were all negative. The Metagenomic Next Generation Sequencing Test in bone marrow was also negative. Antifungal therapy with Voriconazole (Pfizer Inc, New York, NY, USA, 6 mg/kg intravenously every 12 hours for the first 24 hours, then 4 mg/kg oral every 12 hours) instead of amphotericin B was first introduced due to lack of experience with AmB. Trough serum levels of Voriconazole were monitored weekly after 5 days of therapy to ensure adequate absorption, with a goal of

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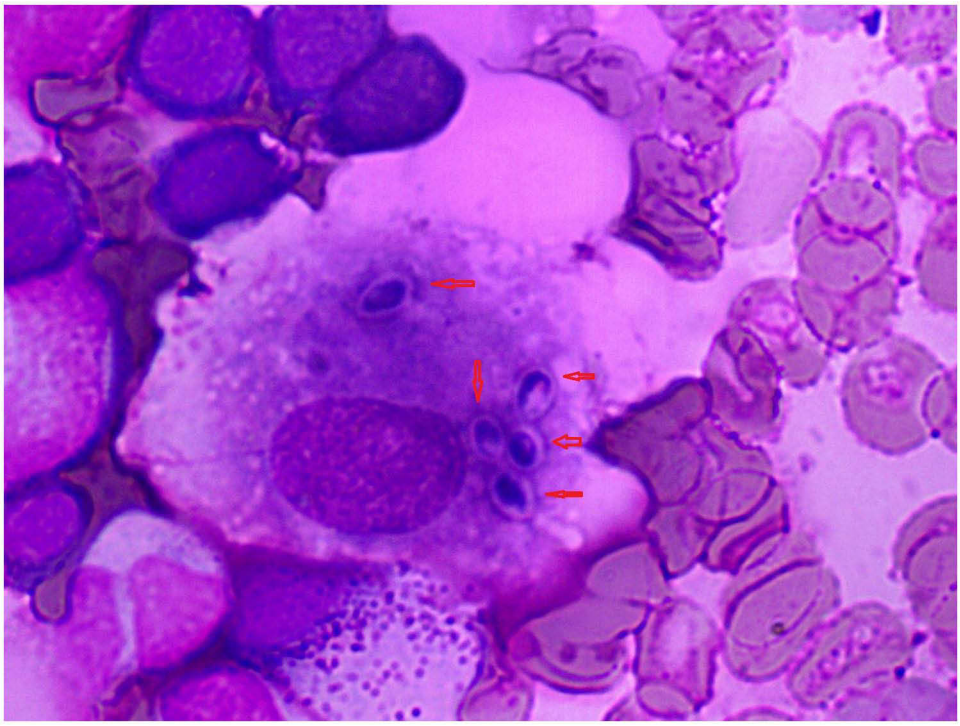

Figure 1 Wright stain finding of bone marrow smear demonstrated intracellular oval budding yeast (red arrows) of *Histoplasma capsulatum*. (1000 × magnification oil lens).

achieving a concentration of 2 to 5μg/mL. 7.40μg/mL,5.29μg/mL, 3.79μg/mL of serum level of Voriconazole were obtained. But the patient did not make improvement. Voriconazole was stopped. Intravenous liposome AmB (New Asia pharmaceutical, Shanghai, China) was gradually added at the dose of 3 mg/kg daily. Two weeks later, the patient's clinical symptoms, such as his fever and loss of appetite, began to improve. But the patient did not tolerate chemotherapy very well with markedly elevated sera creatinine levels. Intravenous AmB liposomal (reduced to 1 mg/kg daily) plus Voriconazole (4 mg/kg oral every 12 hours 4 mg/kg twice daily after initiation of a loading dose) was administered. Monitoring Voriconazole serum levels continued regularly. 0.52μg /mL, 1.71μg/mL, 0.86μg/mL of serum level of Voriconazole were obtained. Glutathione was co-administrated to protecting hepatic and renal function during hospital. The patient with good adherence did not take any agent or food supplements (ie, phenytoin, St.John't wort, etc.) that influenced the blood drug level of Voriconazole. Liposomal AmB (L-AmB) was stopped due to presumption of drug interactions between Voriconazole and AmB. Voriconazole (4 mg/kg oral every 12 hours) alone was administrated for subsequent therapy. 3.20μg /mL, 5.29μg /mL, 4.46μg /mL of serum trough concentration of Voriconazole were obtained, which were significantly higher than previous result. This suggested that AmB may decrease the serum levels of Voriconazole. Unfortunately, due to be unable to test the serum concentration of AmB, we could not observe the influence of Voriconazole on AmB levels.

Sample Collection, Storage and Bio-Analysis

Venous blood samples (2 mL) were collected into anticoagulant tubes. The samples were collected at least 3 days after initiation of a loading dose or maintenance and an adjusted dose of 4 days as well as within 2 h before any maintenance doses.[9] All Voriconazole plasma concentration was measured by an automatic two-dimensional liquid chromatography (2D-HPLC, Demeter Instrument Co., Ltd., Changsha, Hunan, China).[10] The two-dimensional separation conditions consisted of the following: the first dimensional chromatographic column was FRO C18 (100mm × 3.0 mm, 5μm, ANAX); and the flow rate: 1.0 mL/min. The second dimensional chromatographic column was ASTON HD C18 (150 mm × 4.6 mm, 5μm, ANAX). The stability of blood sample at room temperature for 8 h and at-20°C of three repeated freeze-thaw cycles was within ±8.00% and ±10.0%, respectively. Besides, the laboratory performed annual external quality assessment (EQA) to ensure the accuracy of the measurement results.

Discussion

Combination therapy with AmB and Voriconazole is sometimes used due to reducing AmB-related adverse reactions and improving outcomes, especially in refractory invasive fungal infection. However, no study reported whether AmB affected the serum level of Voriconazole. In review of the literature, about eight literature evaluated the therapeutic efficacy of AmB combined with Voriconazole in invasive fungal infection.[1–8] Two reports are in vitro observations,[1,2] three reports are in the animal study,[3–5] and three reports are in patient observation.[6–8] The vitro observations showed combinations antifungal therapy exhibited promising results and no apparent antagonistic interaction was detected. One animal observation indicated that the efficacy of monotherapy and the two-drug combinations therapy was similar; activity was neither enhanced nor reduced with combination therapy. Another two animal studies observed that the AmB + Voriconazole combination was most effective at reducing tissue burden, sterilizing tissues, and reducing mortality than AmB alone or Voriconazole alone. One human observational data showed the triple combination of AmB, caspofungin and Voriconazole may be an option worth exploring in patients with refractory fungal infections who do not appear to be improving on more standard therapy.[6] Another two patients observation demonstrated AmB combined with Voriconazole may rapidly improve clinical manifestation, substantially shorten the hospitalization time.[7,8] The interaction between the two drugs was not mentioned in vivo studies.[1–8] None of them tested the serum level of Voriconazole. Here, we discovered AmB might lower the level of Voriconazole. We observed the serum levels of Voriconazole were in normal levels (7.40μg/mL, 5.29μg/mL, 3.79μg/mL; 3.20μg /mL, 5.29μg /mL, 4.46μg/mL) when Voriconazole was administrated alone. The Voriconazole concentration would be reduced (0.52μg /mL, 1.71μg/mL, 0.86μg/mL) when combined AmB, which indicated AmB might decrease the level of Voriconazole. However, the mechanism underlying is not clear. Voriconazole, an extended spectrum azole, its metabolisation takes place in the liver, at the level of P450 CYP2C19, CYP2C9, and CYP3A4, and its products of metabolism are excreted by the kidneys.[11] Only 2% of the dose excreted in urine is unchanged. There may be a variety of drug–drug interactions that must be considered. AmB is another important drug widely used to treat serious systemic fungal infections. It has a terminal half-life of 127 h in healthy subjects and its distribution differs widely between organs, and the highest AmB concentrations are reached in the liver[12] with the potential to alter hepatic cellular integrity.[13,14] In perfused rat livers, it has been demonstrated that AmB reduces bile flow, decreases bile acid secretion and alter hepatic P-450 activity. Thus, it is possible that AmB affects the level of Voriconazole by altering hepatic p450 activity. But the mechanism needs further research.

Conclusion

In summary, our results showed AmB may decrease the serum concentration of Voriconazole, such a combination of AmB and Voriconazole cannot be considered appropriate until more data are available.

Ethics and Consent

The Ethics Committees of The Second Xiangya Hospital of Central South University (LYF-20221 26) approved this study, the institutional agreed to publish the case details.

Consent for Publication

The patient provided written informed consent for publication of clinical details and images in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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