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CASE REPORT

Liposomal Amphotericin B Induced Acute Reactions

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This study has not been presented in any congress or symposium previously.

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ABSTRACT

Three formulations of amphotericin B are available: liposomal, lipid complex and conventional. The liposomal amphotericin B is more preferred agent than other formulations because of its tolerability, safety and potent antifungal activity. However, the liposomal amphotericin B can cause infusion-related reactions. In this case report, we aimed to report a patient who developed infusion-related reactions during the treatment with the liposomal amphotericin B but eventually tolerated the prolonged infusion. In this case report, we present a patient who developed an infusion-related reaction during The liposomal amphotericin B treatment. A 26-year-old male patient with acute promyelocytic leukemia was hospitalized for the third course of chemotherapy. Due to the invasive fungal infection history in previous hospitalizations, the liposomal amphotericin B 400 mg (IV, 5 mg/kg) once daily was initiated as secondary antifungal prophylaxis. Swelling in infusion site and chest pain were reported within 10 minutes of the liposomal amphotericin B administration, and the infusion rate was slowed down to 400 mg/6 hours from 400 mg/2 hours. All these reactions disappeared with prolonged infusion time. The patient received a total of 7 liposomal amphotericin B doses subsequently without any reaction during the chemotherapy cycle. In our experience, the liposomal amphotericin B-induced infusion-related reactions can be resolved by prolonging the infusion time.

Keywords: Liposomal amphotericin B, infusion-related reactions, amphotericin B deoxycholate, infusion rate.

INTRODUCTION

Amphotericin B is available in formulations of liposomal, lipid complex and conventional. The first three formulations are lipid derivatives more widely used than amphotericin B deoxycholate because of their better tolerability and safety [1]. Liposomal amphotericin B (LAB) is a broad-spectrum antifungal agent that consists of a single bilayer liposomal drug delivery system [1, 2]. Reactions to amphotericin B infusion include nausea, vomiting, fever, chills, and cardiopulmonary events such as chest pain, dyspnea, flushing and hypotension. These reactions usually occur at the onset of infusion and dependent on the rate, but not related to the dose [3]. In a study by Walsh et al., it was found that infusion-related reactions caused by LAB were significantly lower than amphotericin B deoxycholate [4]. Collazos et al. argued that the incidence of amphotericin B deoxycholate-associated pulmonary reactions was higher than amphotericin B lipid complex because of faster infusion rate (2 hours versus 4-6 hours) [1]. In this case report, it was reported a patient who developed infusion-related reactions with LAB but eventually tolerated the prolonged infusion.

CASE PRESENTATION

A 26-year-old, 80 kg, male patient was admitted to the hospital due to the complaints of swelling, increase in fever and pain in his right lower leg and was diagnosed with deep vein thrombosis (DVT). The patient had no comorbidities and allergy history at the time of admission. Enoxaparin was started for DVT treatment. Upon detection of pancytopenia during hospitalization, the patient was consulted with hematologists and diagnosed with acute promyelocytic leukemia. A combination treatment with idarubicin and all-trans retinoic acid (ATRA) were initiated.

Prophylactic antimicrobial regimen with posaconazole (oral, 300 mg daily after initial 300 mg twice a day loading dose on the first day), levofloxacin (oral, 750 mg daily) and valaciclovir (oral, 500 mg twice daily) were also started. On his follow-up, neutropenic fever was developed in patient. Meropenem (intravenous [IV], 1000 mg three times daily) and teicoplanin (IV, a loading dose of 12 mg/kg administered 3 times at 12 h intervals, followed by a maintenance dose of 12 mg/kg daily) were added empirically and for severe mucositis, respectively. On the fifth day of antimicrobial treatment, serum galactomannan index was negative and no growth in fungal cultures, but he was still febrile and computed tomography (CT) of the chest revealed signs of fungal infection. Posaconazole was discontinued and LAB 400 mg (IV, 5 mg/kg) once daily was started for the treatment of invasive pulmonary fungal infection. His status improved, and he recovered from neutropenia. On the fourth week of LAB treatment, repeated chest CT indicated resolution of fungal infection. LAB was stopped and the patient was discharged.

One month later, he was readmitted to the hospital to receive the next chemotherapy course. Due to the prior invasive fungal infection history, LAB 400 mg (IV, 5 mg/kg) once daily was initiated as secondary antifungal prophylaxis. However, chest pain and swelling in infusion site were reported within 10 minutes of LAB administration on the 2nd day of treatment. LAB infusion was stopped because infusion-related reaction was suspected. No therapy was given to the patient to relieve infusion-related reactions. After the improvement of patient's symptoms, LAB treatment was restarted by slowing the infusion rate from 400 mg/2 hours to 400 mg/6 hours. All these reactions disappeared with prolonged infusion. The patient received a total of 7 LAB doses subsequently without any reaction during the chemotherapy cycle. Thereafter, LAB administration with prolonged infusion during his next chemotherapy course was also completed without any reactions.

DISCUSSION

In this case report, we present a patient who received 2 hours infusion of 400 mg (IV, 5mg/kg) LAB and developed infusion-related adverse reactions including swelling in the infusion site and chest pain. These reactions disappeared when the infusion rate was prolonged to 6 hours.

The use of conventional amphotericin B is restricted by the high incidence of infusion-related adverse events and nephrotoxicity. Alternative formulations have been developed to minimize

the toxicity and adverse effects and to increase the therapeutic index of the drug [5]. Published safety data provided by the manufacturer and data from a multicenter phase II/III study evaluating over 100 treatment episodes with LAB showed increased tolerability and significantly reduced toxicity compared with conventional amphotericin B [6]. However, in the literature, infusion-related adverse reactions with LAB have been rarely reported [7]. A possible relationship between the infusion rate of LAB and adverse effects has not been studied sufficiently. Animal studies have shown that amphotericin B directly damages endothelial cells in a dose and time-dependent manner, irrespective of the vehicle (deoxycholate) [8]. It also alters neutrophil functions [9], induces neutrophil-independent lung damage associated with oxidative stress and eicosanoid production [10], causes lung dysfunction through the release of cyclooxygenase products of arachidonic acid metabolism [11, 12].

In a case series, LAB was administered at a dose of 3 mg/kg/day over 1-hour infusion in 3 patients. The first patient developed chest tightness and difficulty of breathing, the second patient developed dyspnea and acute hypoxia 10 minutes after the onset of the infusion. The third patient developed chest pain at the fifth minute of the infusion. Two of these patients tolerated LAB when infusion rate was extended to 2 hours and with administration of meperidine. To avoid adverse reactions, at least two hours of LAB infusion was recommended [11]. Package insert of LAB approved by the Food and Drug Administration (FDA) had a few reports of chest pain, flushing, back pain with or without chest tightness after LAB administration. However, infusion-related reactions were reported to be very rare, mostly developed shortly after the onset of infusion and disappeared with slower infusion rates [13].

It is recommended that the first infusion of LAB should be administered slowly under observation, and the patient should be specifically asked about the presence of even mild symptoms on the first days of treatment. If acute respiratory symptoms develop during administration of LAB, the infusion should be stopped immediately to prevent further clinical deterioration. If treatment with LAB is to be continued, the patient should be closely monitored for re-exposure, the infusion rate should be slowed down and symptomatic treatment should be considered if necessary [1]. However, the exact duration of the slow infusion rate is not clear. The product information reported by FDA suggested that 60 minutes infusion rate could be initiated for patients who could tolerate treatment with 120 minutes [13]. In a study by Schöffski et al., any difference was not observed between 1 and 4 hours of infusion time in terms of pulmonary toxicity [14]. Collazos et al. reported that no further symptoms were developed when the infusion time was increased to 6 hours in a patient who had symptoms while receiving amphotericin B lipid complex (3 mg/kg/day) over for 2 hours [1].

In our patient, infusion-related reactions developed shortly after the onset of LAB infusion. Based on studies by Schöffski et al. [14], and Collazos et al. [1], we extended the infusion time to 6 hours instead of 2 hours. The symptoms disappeared when the infusion rate was slowed down.

In summary, infusion-related reactions with LAB appear to occur rarely. However, these symptoms can sometimes be life-threatening. Even though some reports indicate that the infusion rate does not provide relief from symptoms whether the drug was given in 1 hour or 4 hours, we recommend based on our case, infusion of LAB be over 6 hours and careful monitoring was provided.

Key Points

Even though infusion-related reactions with liposomal amphotericin B appear to occur rarely, these symptoms can sometimes be life-threatening.

Some reports indicate that the infusion rate does not provide relief from symptoms whether the drug was given in 1 hour or 4 hours.

In this study, the infusion of LAB over the course of 6 hours was recommended to remain on the safe side with careful monitoring.

CONFLICT of INTEREST STATEMENT

No, there is no conflict of interest that I should disclose, having read the above statement.

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