Case Report / Olgu Sunumu

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Reasons for Failure of Antifungal-lock Therapy with Caspofungin: Need for Higher Concentrations

Kaspofunginle Antifungal Kilit Tekniği Başarısızlık Nedenleri: Daha Yüksek Konsantrasyon İhtiyacı

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Abstract

Antifungal-lock therapy (AfLT) has arrived as an investigational approach for preventing catheter removal with limited clinical evidence of its efficiency. The principle of AfLT consists of catheter lumen replenishment by a selected antimicrobial agent and then locking it for an alternative treatment to eradicate the microbes embedded in endoluminal biofilms. Herein, we report a pediatric hematology-oncology patient with *Candida parapsilosis*-related central venous access device infection in which catheter removal was performed despite the systemic and intraluminal caspofungin treatment. For now, we recommend higher doses of caspofungin for AfLT especially in *Candida parapsilosis*-related catheter infections.
Keywords: Antifungal-lock technique, *Candida* species, caspofungin, catheter

Öz

Antifungal kilit tekniği (AfKT) kateter çıkarılmasını engellemek amacı ile etkinliği hakkında kısıtlı verinin olduğu bir deneysel yaklaşım olarak karşımıza çıkmaktadır. Bu teknikte endoluminal biyofilmler içine gömülü olan etkenlerin eradike edilmesi için katater lümeni, seçilen antimikrobiyal ajanla doldurularak kapatılır. Burada yoğun bakım servisimizde yatan ve *Candida parapsilosis* ilişkili santral venöz kateter enfeksiyonu olan bir hematoloji-onkoloji hastasından gerek intraluminal gerekse sistemik kaspofungin tedavisine rağmen kateteri çıkartmak zorunda kalışımızı raporladık. Özellikle *Candida parapsilosis* ilişkili kateter enfeksiyonlarının AfKT ile tedavi edilebilmesi için daha yüksek dozda kaspofungin kullanılmasını önermekteyiz.
Anahtar Kelimeler: Antifungal kilit tekniği, *Candida* türleri, kaspofungin, kateter

Introduction

The incidence of fungal infections in pediatric patients follows the same trend of increase as in adults.[1] Among them, *Candida* species have been the dominant type representing the majority of blood stream infections (BSI) and associated catheter-related BSI with a rate of 10%.[2] Recent studies have reported increased incidences of other *Candida* species, especially *Candida parapsilosis* besides *Candida tropicalis* and *Candida glabrata*.[3] *Candida parapsilosis* is a major concern since its association with central venous access device (CVAD)-related infections has been well demonstrated.[3] The Infectious Diseases Society of America (IDSA) and European Society for Clinical Microbiology and Infectious Diseases guidelines on *Candida* catheter-related BSI recommend systemic antifungal therapy and timely catheter removal.[4,5] However, catheter removal may not be easily performed in real life. First of all; removal from patients with totally implanted catheters, such as ports, require a surgical procedure. Moreover, patients' co-morbidities, such as severe thrombocytopenia and disseminated intravascular coagulation, could complicate the process. Antifungal-lock therapy (AfLT) is an investigational approach which can be used as salvage therapy for preventing catheter removal.[5] The principle of AfLT consists of catheter lumen replenishment by a selected antimicrobial agent and

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then locking it for an alternative treatment to eradicate the microbes in endoluminal biofilms. The most promising AfLT include ethanol, amphotericin B or echinocandins.[6] Among them, *Candida parapsilosis* requires special considerations, since there were some reports of decreased susceptibility to systemic echinocandins.[7] The feasibility of caspofungin for AfLT is still an unanswered question for the clinicians. Herein, we report a pediatric hematology-oncology patient with *Candida parapsilosis*-related central venous access device (CVAD) infection in which the catheter was removed despite systemic and intraluminal caspofungin treatment. Written informed consent was obtained from the parent of the patient.

Case

A 1.5-year-old boy with pro-B acute lymphoblastic leukemia was transferred to the pediatric intensive care unit (PICU) due to *Enterobacter cloacae* septicemia, respiratory failure and septic shock. The patient was treated with intravenous meropenem and amikasin. He had a long-term CVAD (port) for 10 months. The white blood count was 900 mm^{-3}, neutrophil count was 150 mm^{-3}, and platelet count was 19000 mm^{-3}. On the 43th day of admission to the PICU, blood cultures, two from peripheral veins and one through ports, revealed *Candida parapsilosis* growth which was susceptible to caspofungin, and amphotericin B. Since *Candida parapsilosis* was isolated under liposomal amphotericin B therapy, previous antifungal therapy was ceased and intravenous caspofungin (70 mg/m^2 on the first day and 50/m^2 for maintenance therapy) was initiated. The blood cultures from peripheral veins revealed no isolation of *Candida parapsilosis* on the 4th day of caspofungin therapy, however, consecutive blood cultures revealed *Candida parapsilosis* isolation. We could not remove the catheter due to the patient's clinical status and absence of any other available vascular access. AfLT with caspofungin was also initiated on the 7th day of intravenous caspofungin. The lock used a portion of 3 mL solution of 10 mg of caspofungin and 5% dextrose with 200 units of heparin and placed lines for 12 h. AfLT was repeated at every 12 hours and the catheter blood culture was taken before each procedure as described before.[8] On the 14th day of AfLT, since no negative culture could be achieved with AfLT, the port was removed.

Discussion

There is currently no consensus on the treatment of invasive *Candida parapsilosis* infections, although the therapeutic approach typically includes the extraction of any removable foreign bodies and the administration of systemic antifungals.[4] The IDSA guidelines list amphotericin B, fluconazole, and caspofungin as therapeutic options for the treatment of candidemia.[4] The reports of successful AfLTs have been reported more and more frequently with different agents, however, we had experienced a treatment failure which led to removal of the catheter despite intraluminal and systemic caspofungin treatment.

Biofilms are surface-associated communities of microorganisms within an extracellular matrix and are the most prevalent type of microbial growth.[9] Although *Candida parapsilosis* has been reported to produce quantitatively and structurally less complex biofilm than *Candida albicans*; *Candida parapsilosis* biofilms can occur on medical devices, including central venous catheter (CVC) and peripheral venous catheters.[10] The formation of biofilms is important for the failure of AfLT; since it is one of the major virulence factors resulting in significant resistance to antifungal therapy by limiting the penetration of substances through the matrix and protecting cells from host immune responses. There are extensive data demonstrating the resistance of *Candida* species in biofilms to antimycotic drugs.[11]

Therapeutic levels of echinocandins can inhibit metabolic activities of *Candida parapsilosis* biofilms[9], and lipid formulations of amphotericin B have shown activity against *Candida parapsilosis* biofilm.[9] However, *in vitro* studies with high-dose amphotericin B usage demonstrated that biofilms of *Candida parapsilosis* were inhibited to a lesser extent compared to *Candida albicans* and *Candida glabrata*.

Devrim et al.[12] published an article in 2016 and they pointed out that 15 of 41 patients with *Candida parapsilosis* blood stream infection, who had CVC, were treated with caspofungin without the need for catheter removal. However, caspofungin was not used in lock therapy. It was used systematically in that study.

There are limited reports which had focused on caspofungin and its concentration for intraluminal usage. Thus, the optimal concentration has not been determined yet. Previous reports including *in vitro* studies have reported caspofungin usage as a wide spectrum of concentration ranging from 0.00025 mg/lt to 25 mg/lt for a wide spectrum of duration of therapy ranging from 6 hours to 48 hours.[13,14] However, only one report is available for the intraluminal caspofungin therapy with a dosage of 3.33 mg/mL in a 9-year-old child for the treatment of *Candida lipolytica* fungemia-associated catheter infections.[9] In this report, the negative culture was achieved after the fourth day, however, we could not rescue the catheter despite 14 days of intraluminal therapy with caspofungin at the same dose. This could be due to the decreased susceptibility to caspofungin since caspofungin minimal inhibitory concentration (MIC) for *Candida parapsilosis* are higher than those for other *Candida* species, with average MIC_{50} and MIC_{90} values ranging between 0.85

and 2 g/mL and 2 and 2.33 g/mL, respectively.[15] According to our experience; higher concentrations of caspofungin might be required for AfLT for *Candida parapsilosis*.

Since there is inadequate clinical data for forming the base for specific recommendations for AfLT in the management of catheter-related infections and lack of standardization of the dosage, duration and intraluminal time spent; randomized clinical trials are essential. There should be further studies exploring the appropriate caspofungin dose for AfLT in catheter infections associated with *Candida parapsilosis.*

Ethics

Informed Consent: Written informed consent was obtained from the parent of the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.C., Ö.S., F.S., Concept: G.C., F.S., Design: H.A., İ.D., Data Collection or Processing: R.İ., Ö.S., Analysis or Interpretation: H.A., İ.D., B.D., Literature Search: G.G., G.C., Writing: G.C., R.İ.

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