Review

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Experience of micafungin in patients requiring extrarenal depuration

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ABSTRACT

Introduction. The use of extrarenal depuration techniques is increasingly frequent in patients admitted to the ICU. The use of these techniques has been linked to a decrease in plasma concentrations of several antimicrobials, including fluconazole. The activity of antifungal agents is dependent on obtaining adequate concentrations in the plasma and at the site of infection. Micafungin is a new antifungal drug recently introduced in our country.

Objective. To review the published experience of pharmacokinetic (PK) parameters of micafungin in patients requiring some type of extrarenal depuration technique during their stay in the ICU.

Results. Three studies were identified with data on PK parameters of micafungin during the use of continuous venovenous haemodialysis (CVVHD) (2 publications) and continuous haemodiafiltration (CHDF) (1 publication). In all of them, minimum variations in the plasma concentration of micafungin at the entry and exit sites of the haemofilter and nil or minimal presence of micafungin in the ultrafiltration fluid were demonstrated.

Conclusions. No adjustment of the dose or interval between doses of micafungin during the use of extrarenal depuration techniques in critically ill patients admitted to the ICU is necessary.

Key words: micafungin, extrarenal depuration techniques, ICU

INTRODUCTION

The efficacy of an antimicrobial depends, among other factors, on its ability to provide at the infection site a sufficient concentration to inhibit the growth of the microorganisms responsible for the infectious process. The concentration of an antimicrobial in the tissues is determined by numerous factors, in particular its volume of distribution, metabolism and excretion kinetics which gives rise to a set of pharmacokinetic (PK) variables used to determine the differential characteristics with others drugs in the same or other families of antimicrobials[1,2].

Patients who develop a fungal infection as a result of treatment with antifungals frequently present with serious conditions with multiple organ or system failure that require mechanical or pharmacological replacement. One of the most frequent complications is renal failure for which patients require extrarenal depuration systems to treat it. This name comprises a set of techniques of great complexity and functional variability aimed at replacing impaired renal function with filtration systems that remove the toxic products which have accumulated in the blood[3]. During the application of these techniques, some of the drugs administered for the treatment are also extracted, altering their plasma concentration which can affect efficacy.

Micafungin is a new antifungal approved by the regulatory agencies for medicinal products in the treatment of invasive candidemias and candidiasis and oesophagitis due to *Candida* spp and for the prophylaxis of patients with haematopoietic transplants[4,5]. Its effectiveness is confirmed by a series of well established pharmacokinetic and pharmacodynamic reports (PK/PD reports)[6,8] (table 1) and that may be altered during the application of extrarenal depuration techniques.

This paper is a review of the different techniques used in extrarenal depuration, the factors that affect the elimination of the drugs during their application and, specifically, the impact of the various extrarenal depuration techniques on the plasma levels of micafungin.

CLASSIFICATION OF THE EXTRARENAL DEPURATION TECHNIQUES

The aim of extrarenal depuration techniques (EDT) is to carry out the two basic functions of the kidneys: the elimination of toxic or unnecessary substances and control of

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the fluid balance. Using a venous catheter and peristaltic pump, the patient's blood is drawn and circulated through an extracorporeal circuit, then returning it to the patient after passing through the authentic "glomerule" of the system which is the filter. The filter consists of a semi-permeable membrane which allows water and all the molecules with a molecular weight (MW) < 60,000 Daltons (Da) to pass freely.

To achieve the solute and water interchange through the membrane, different physical principles can be used: a) *Ultrafiltration*, also called convective transport, consists of the simultaneous passage of water and solutes through the membrane under the effect of a hydrostatic pressure gradient. Molecules with a medium-high molecular weight (ultrafiltered) are eliminated. b) *Diffusion* or diffusive transport is the passive movement of solutes through the membrane owing to the difference in the concentration gradient between the blood and dialysis fluid until parity is achieved between the blood and fluid concentration. Molecules with low molecular weight are eliminated. c) In both cases another physical mechanism can be activated called *adsorption* whereby certain solutes adhere to the membrane of the dialyser. Adsorption is more evident on polysulfone and acrylonitrile membranes than on cellulose membranes.

Table 1 Pharmacokinetic parameters of micafungin

Cmax	10.1 mg/l (100 mg/day) 16.4 mg/l (150 mg/day)
AUC	115 mg h/l (100 mg/day) 167 mg h/l (150 mg/day)
Clearance	~0.3 ml/min/kg
Half life (t½)	15-17 h
Volume of distribution	0.39 l/kg
Protein binding	>99%
Molecular weight	1,292.3
Metabolism	Hepatic
Faecal elimination	71%
Urine elimination	1%

Cmax: Maximum concentration; AUC: Area under curve

Depending on the type of membrane, the dialysis solutions, the physical depuration principle and the time taken by the technique, the different depuration techniques are obtained: Intermittent haemodialysis (IHD), Continuous Extrarenal Depuration Techniques (CEDT).

IHD applies the physical principle of diffusion, being a very effective treatment and it is therefore feasible to carry out depuration over short periods of time, but this is very aggressive and poorly tolerated by the critical patient.

CEDTs are based on continuous ultrafiltration methods using convection (haemofiltration) as the principal depuration mechanism, and diffusion can also be used if the dialysis fluid is made to flow counter current (haemodiafiltration). Depending on the combination used in CEDTs, we can use different therapies: Slow continuous ultrafiltation (SCUF), High volume haemofiltration (HVHF), Continuous haemodialysis (CHD), Continuous haemodiafiltration (CHDF) and High flow haemodialysis (HFD)[3].

The characteristics of the membrane used are critical for achieving optimum permeability and biocompatibility. It is very important that the membrane is biocompatible, especially in CEDT since the time the blood is in contact with the membrane can cause activation of different biological systems such as complement activation, leukocyte aggregation, stimulation of the production of cytokines and other pro-inflammatory cytokines, all of which can cause an intolerance to the depuration process[9].

At the same time, the membranes can be classified according to their inherent characteristics of permeability to water and solutes. Permeability to water is expressed as an ultrafiltration coefficient (UFC), with UFC membranes of < 10 ml/h/mmHg being considered as low permeability and UFC membranes of >10 ml/h/mmHg being considered as high permeability. The permeability of solutes will depend on the size of the membrane pores.

FACTORS INVOLVED IN THE DEPURATION OF MOLECULES DURING EXTRARENAL DEPURATION TECHNIQUES

The basic principles relating to the elimination of molecules and drugs through the membrane in EDT are linked to convection and diffusion transport.

The intrinsic factors of these molecules are: a) the MW since, in order to pass through the membrane, it must be smaller than the cut-off point of the membrane; b) the protein bound molecule fraction, as it will be a limiting factor for crossing the membrane; c) the volume of distribution (Vd) which reflects the amount of drug administered to the patient to obtain a specific blood concentration such that the greater the Vd the lower the proportion of drug in the central compartment and less significant will be the quantity eliminated by means of extracorporeal circuits[10]; and d) lastly, it will be the clearance fraction (CFI) of the molecule that determines whether EDT may involve a change to the dosing of a particular drug.

Therefore, the molecules with potential significant elimination via the EDTs are those with a low MW, low protein binding, low volume of distribution and poor elimination by other routes of excretion.

The elimination of molecules will also vary depending on the physical principle of depuration used in the depuration technique. a) Diffusion: the diffusion rate is directly proportional to the product of the concentration gradient and surface area of the membrane, the proportionality constant is known as the diffusion coefficient. The diffusion coefficient increases with temperature

and diminishes with viscosity and MW. The molecules that can be easily transported by this mechanism are those with a MW <500 Da. b) Convection: creating a transmembrane pressure gradient (TPG), some plasma water is extracted together with the molecules that are below the size of the membrane pores (40,000-50,000 Da). The small and medium calibre molecules can be transported by this mechanism. To measure the haemofiltration the concept of Filtration Factor (FF) must be understood. This is the percentage of serum ultrafiltered from the total plasma and which passes through the filter in a specific time. The recommended FF is less than 25%.

EXTRARENAL DEPURATION TECHNIQUES IN ICU

There is no specific record of the use of EDT in patients admitted to the ICU. However, the ENVIN-ICU register created to control ICU acquired infections and the consumption of antimicrobials during patient stay in these departments has included amongst its variables, since 2006, the use of extrarenal depuration. Table 2 shows the trend over the last 4 years, indicating a constant increase in the use of these techniques[11].

PHARMACOLOGICAL CHARACTERISTICS OF MICAFUNGIN

Micafungin is a semi-synthetic cyclical derivative of a natural compound (FR901379) produced by the fungus *Coleophoma empetri*[12]. Specifically, it is a cyclical amphiphilic hexapeptide with a N-acyl lipophil chain which seems to give micafungin greater antifungal potency than the other echinocandins[13]. It also has an amine group which links the radical 3-hydroxy-4-methylproline to the amine group in the delta position of the dihydroxyornithine group to form a ring[14]. It has a high molecular weight (1,292.26 Da). It comes in the form of a hygroscopic photosensitive powder, similar to the acetate of caspofungin and with good solubility in water and saline solution[15].

Micafungin acts by inhibiting the formation of the enzyme β-1,3-D glucan synthase which is the enzyme necessary for the synthesis of β-1,3-D glucan, a glucose polymer needed to maintain the integrity of the cell wall of the majority of pathogenic fungi. Micafungin has concen tration dependent fungicidal activity, against the majority of species of *Candida* and *Aspergillus*.

Its pharmacokinetic parameters have been studied in different populations, including patients with severe renal failure[6]. Its reference values are shown in table 1[16,17]. Micafungin is not absorbed orally, has a dose-dependent linear kinetic profile, reaches the steady state between day 4 and day 5 after repeated dosing and is widely distributed in the lungs, liver, spleen and kidneys, but not in the central nervous system. It is more than 99% protein bound. It is metabolised in the liver via a route that does not include cytochrome P-450 and is eliminated inactive via the bile, with 43.8% of the drug being found in the faeces.

Based on various experiences described in the literature, it has been suggested that the PK/PD properties of echinocandins, including micafungin, allow longer dosing regimen intervals of these antifungals[17]. This means that echinocandins can be administered on alternate days, or even weekly. However, these proposals were based on the results of previous *in vitro* studies which need to be confirmed by experiments in humans.

Table 2 **Trend of extrarenal depuration techniques in patients admitted to the ICU for more than 24 hours (ENVIN data 2006-2009)[11]**

	2006	2007	2008	2009	TOTAL
ICU patients, nº	11.684	12.453	13.824	14.983	52.944
Patients with EDT	407	540	668	769	2.384
Level of use of EDT	3,48	4,34	4,83	5,13	4,50

EDT: Extrarenal depuration techniques

A study based on time-kill curves showed that micafungin has an essentially fungicide activity[18]. This antifungal drug generated a reduction of more than 99.9% in the cfu number of isolates of *C. albicans, C. glabrata* and *C. krusei.* However, the effect was fungistatic against *C. tropicalis*. Micafungin showed a fungicidal concentration and dose-dependent activity against strains of *C. albicans* in neutropenic rabbits with disseminated candidiasis, with a significant reduction in the *C. albicans* load in various tissues[19]. Some experiments have shown that the increased dose of micafungin leads to a reduction in mortality in animal models of candidiasis and aspergillosis[15] However, it was not possible to demonstrate a reduction in the fungal load in the tissues with an increase in the dose of micafungin.

The objective of one study was to carry out a PK/PD analysis to assess the various dosing guidelines of micafungin in the treatment of *Candida* and *Aspergillus* infections in haematological patients[20]. For PK/PD modelling, blood samples were obtained from patients treated with doses of micafungin between 50 and 300 mg. The results showed that in the case of *Candida* infections, the approved doses for micafungin used in prophylaxis and treatment achieved the PK/PD objectives commonly considered to be optimum. Specifically, an AUC/MIC ratio of free fraction of micafungin was obtained equal to 10 (fungistatic effect) and 20 (fungicidal effect) with a probability above 95%. In the case of *Aspergillus*, it is thought that the effect of micafungin is concentration dependent. In this experiment and on the basis of previous studies, it appears necessary to obtain free plasma concentrations of 0.05 mg/l (with a 99% plasma protein binding expectation). The probability of achieving this objective was 80% when doses of 200 mg were used.

CLINICAL EXPERIMENTS OF MICAFUNGIN IN PATIENTS WITH EXTRARENAL DEPURATION TECHNIQUES

Micafungin is the echinocandin on which there is most information on the effect of the use of extrarenal depuration techniques in the PK/PD parameters.

In 2004, Kishino S et al.[21] studied the effect of continuous veno-venous haemodialysis (CVVHD) on liver transplant recipients who received prophylatic micafungin in order to optimise dosing. Six liver transplant patients were included and admitted to an ICU in Japan. 40-50 mg/day of micafungin were administered in a continuous infusion of 60 minutes for 3 weeks. The CVVHD was performed using a cellulose triacetate dialyser of 1.5 m^2 . The filtrate flow was 100 ml/min and a constant ultrafiltrate of 2,000 ml/hour was obtained. Samples were taken to calculate the PK/PD variables on the third day after the start of administration. The parameters were calculated on the basis of an open-label, two compartment model. The peak concentrations (Cmax) and trough concentrations (Cmin) were 6.31 ± 1.08 and 1.65 ± 0.54 mg/l, respectively. In previous studies in laboratory animals[22] it was reported that the minimum plasma concentrations associated with therapeutic effectiveness in invasive candidiasis and aspergillosis were between 0.16-0.26 mg/l and 0.55-0.80 mg/l, respectively. The half-life was 13.63 hours and the area under curve was 50.04 mg h/l. The micafungin concentrations on entry and exit from the haemodialysis filter were very similar (figure 1). The mean ratio of the concentration of micafungin on entry and exit was 0.96 ± 0.4 and the micafungin clearance was 0.054 ±0.04 mg h/l. The total quantity of micafungin recovered in the ultrafiltrate was 1.0 mg. Alongside these pharmacokinetic findings, micafungin was effective in preventing systemic fungal infections in liver transplant patients. No dosage adjustment or change to the administration intervals of micafungin were necessary during CVVHD.

Micafungin has been used for the treatment of peritonitis due to *Candida parapsilosis* in a female patient undergoing veno-venous haemodialysis[23]. This was a 49 year old female patient with chronic kidney failure secondary to Goodpasture syndrome and in outpatient continuous peritoneal dialysis. She was admitted to hospital for fever and abdominal pain and diagnosed with peritonitis following clinical examination and laboratory tests. The initial antibiotic treatment did not improve the clinical condition and when *C. parapsilosis* was identified in the dialysis fluid, fluconazole treatment was initiated (400 mg/day) with poor clinical response. Therefore the antifungal was changed to micafungin and the peritoneal dialysis catheter was removed. Clinical response was excellent with a diminution of the beta-D glucan marker from 106 to 12.6 pg/ml, which enabled the patient to recover. Although there are no

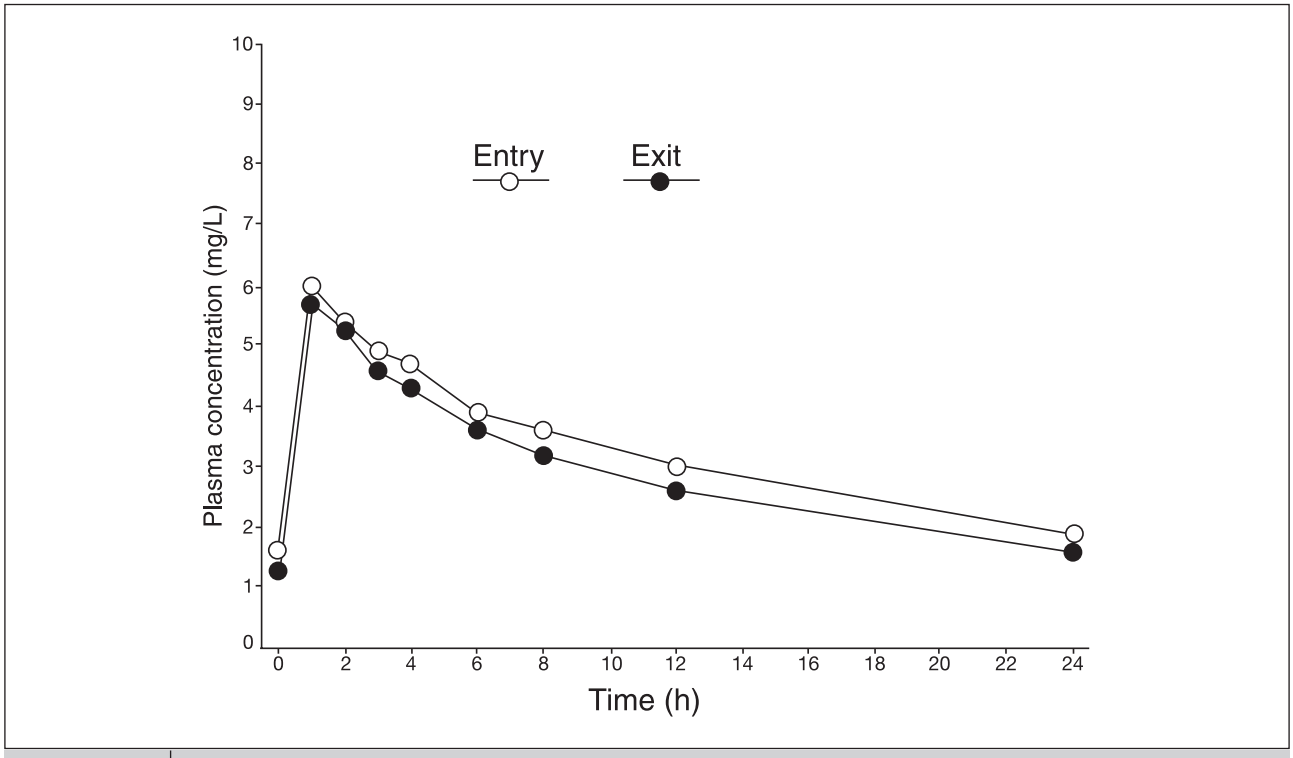

Figure 1 | **Micafungin concentrations on entry and exit from the haemodialysis filter (source: Kishino S, et al.[21])**

pharmacokinetic studies on fluconazole and micafungin, it is possible that the plasma levels and secondarily the abdominal cavity levels of fluconazole were not sufficiently high to achieve eradication of the pathogen causing the peritonitis.

Later in 2006, Hirata et al.[24] designed a study to evaluate the impact of CHDF in the pharmacokinetic parameters of micafungin in critical patients admitted to the ICU. For this purpose, four patients receiving CHDF were included and a further nine who were not receiving CHDF. Doses of 150-300 mg/day were given at the discretion of the doctor in charge of the patients and not at that of the study investigators. For the CHDF a polymethyl methacrylate membrane cartridge was used. The blood infusion rate through the membrane was 1.5 ml/kg/minute. The standard dialysis fluid was pumped at a rate of 500-1,000 ml/hour. An ultrafiltrate flow rate between 800 and 1,300 ml/hour was achieved. The evaluation criterion used was the concentration ratio of micafungin in the serum divided by the body weight (C/D). The micafungin plasma concentrations on entry and exit from the filtrate circuit, in the ultrafiltrate fluid and urine were 12.7 ± 10.2 mg/l, 12.3 ± 10.1 mg/l, undetected and 0.2 ± 0.1 ml/l respectively. The results of the study showed that there was no gradual accumulation or elimination of micafungin in patients using CHDF. The mean micafungin extraction rate, expressed as a percentage, during CHDF was 3.6 ± 3.9. There were no significant differences in the plasma concentration of micafungin expressed by the C/D ratio between patients who received CHDF and those who did not, leading to the conclusion that no dosage adjustment of micafungin is necessary during the use of this technique.

In conclusion, the clinical data known to date show that micafungin can be administered to critical patients requiring haemodialysis or continuous haemodiafiltration without the need to alter the recommended doses or intervals.

REFERENCES

1. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005; 44:1009-34
2. Scaglione F, Paraboni L. Pharmacokinetics/pharmacodynamics of antibacterials in the Intensive Care Unit: setting appropriate dosing rgimes. Antimicrob Agents Chemother 2008; 32:294-301
3. Uchino S, Bellomo R, Morimatsu H, Morguera S, Schetz M, Tan I et al. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. Kidney) investigators. Intensive Care Med 2007; 33:1563-70
4. Micafungina. Ficha técnica o resumen de las características del producto. En: http://ec.europa.eu/health/documents/community-register/2008/20080425431l0/anx_43110_es.pdf. (Ultima consulta 15 de julio 2010)
5. Bormann AM, Morrison VA. Review of the pharmacology and clinical studies of micafungin. Drug Design Develop Ther 2009; 3:295-302
6. Hebert MF, Smith HE, Marbury TC, Swan SK, Smith WB, Townsend RW et al. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. J Clin Pharmacol 2005; 45:1145-52
7. Catalán-Gonzalez M, Montejo-Gonzalez JC. Farmacodinamia y farmacocinética de la micafungina en adultos, niños y neonatos. Rev Iberoam Micol 2009 ; 26:23-34
8. Kim R, Khachikian D, Reboli AC. A comparative evaluation of properties and clinical efficacy of the echinocandins. Expert Opin Pharmacother 2007; 8:1479-92
9. Opatrný K. Clinical importance of biocompatibility and its effect on haemodialysis treatment. Nephrol Dial Transplant. 2003; 18 suppl 5:v41-4
10. Bressolle F, Gonçalves F, Gouby A, Galtier M. Clinical pharmacokinetics during continuous haemofiltration. Clin Pharmacokinet 1994; 26:45-471
11. Estudio Nacional de Vigilancia de Infección Nosocomial (ENVIN-UCI). Sociedad Española de Medicina Intensiva y Unidades Coronarias. Informe de los años 2006, 2007, 2008 Y 2009. En: http://hws.vhebron.net/envin-helics/ (Ulltima consulta 15 de julio del 2010)
12. Tawara S, Ikeda F, Maki K, Morishita Y, Otomo K, Teratani N et al. In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. Antimicrob Agents Chemother 2000; 44:57-62
13. Borman AM, Morrison VA. Review of the pharmacology and clinical studies of micafungin. Drug Design Develop Ther 2009; 3:295-302
14. Debono M, Gordee RS. Antibiotics that inhibit fungal cell wall development. Ann Rev Microbiol 1994; 48:471-97
15. Wiederhold NP, Lewis II JS. The echinocandin micafungin : a review of the pharmacology, Spectrum of activity, clinical efficacy and safety. Expert Opin Pharmacother 2007; 8:1155-66
16. Joseph JM, Jain R, Danziger LH. Micafungin : a new echinocandin antifungal. Pharmacotherapy 2007; 27:53-67.
17. Sucher AJ, Chachine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother 2009; 43:1647-57
18. Ernst E, Roling E, Petzold CR, Keele DJ, Klepser ME. In vitro activity of micafungin (FK-463) against Candida spp : microdilution, time-kill, and postantifungal-effect studies. Antimicrob Agents Chemother 2002; 46:3846-53
19. Petraitis V, Petraitiene R, Groll AH, Roussillon K, Hemmings M, Lyman CA et al. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK 463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. Antimicrob Agents Chemother 2002; 46:1857-69
20. Ikawa K, Nomura K, Morikawa N, Ikeda K, Taniwaki M. Assessment of micafungin regimens by pharmacokinetic-pharmacodynamic analysis : a dosing strategy for Aspergillus infections. J Antimicrob Chemother 2009; 64:840-4

21. Kishino S, Ohno K, Shimanura T, Furukawa H, Todo S. Optimal prophylactic dosage and disposition of micafungin in living donor liver recipients. Clin Transplant 2004; 18:676-80
22. Wakai Y, Ushitani T, Matsumoto S, et al. Minimun effective concentrations of micafungin for the treatment of disseminated Candida albicans infection and pulmonary Aspergillus fumigatus infection in mouse. Jpn J Chemother 2002; 50:43
23. Hirata K, Aoyama T, Matsumoto Y, Ogawa F, Yamazaki H, Kikuti A et al. Pharmacokinetics of antifungal agent micafungin in critically ill patients receiving continuous hemodialysis filtration. Yakugaku Zasshi 2007; 127:897-901.
24. Hasimoto H, Moriya R, Kamata K, Higashilara M, Yoshida K, Kume H. Successful treatment with micafungin (MCFG) of severe peritonitis due to Candida parapsilosis with chronic renal failure patient on hemodialysis. Kansenshogaku Zasshi J Jap Assoc Infect Dis 2005; 79:195-200