Experience of micafungin in patients requiring extrarenal depuration

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.12

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 transplants4. Its effectiveness is confirmed by a series of well established pharmacokinetic and pharmacodynamic reports (PK/PD reports)6 (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
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.

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 ultrafiltration (SCUF), High volume haemofiltration (HVHF), Continuous haemodialysis (CHD), Continuous haemodiafiltration (CHDF) and High flow haemodialysis (HFD).

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.

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; 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.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pharmacokinetic parameters of micafungin</th>
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</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>10.1 mg/l (100 mg/day)</td>
</tr>
<tr>
<td></td>
<td>16.4 mg/l (150 mg/day)</td>
</tr>
<tr>
<td>AUC</td>
<td>115 mg h/l (100 mg/day)</td>
</tr>
<tr>
<td></td>
<td>167 mg h/l (150 mg/day)</td>
</tr>
<tr>
<td>Clearance</td>
<td>-0.3 ml/min/kg</td>
</tr>
<tr>
<td>Half life (tv)</td>
<td>15-17 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.38 l/kg</td>
</tr>
<tr>
<td>Protein binding</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>1,292.3</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Faecal elimination</td>
<td>71%</td>
</tr>
<tr>
<td>Urine elimination</td>
<td>1%</td>
</tr>
</tbody>
</table>

Cmax: Maximum concentration; AUC: Area under curve
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

<table>
<thead>
<tr>
<th>Year</th>
<th>ICU patients, n°</th>
<th>Patients with EDT</th>
<th>Level of use of EDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>11,684</td>
<td>407</td>
<td>3,48</td>
</tr>
<tr>
<td>2007</td>
<td>12,453</td>
<td>540</td>
<td>4,34</td>
</tr>
<tr>
<td>2008</td>
<td>13,824</td>
<td>668</td>
<td>4,83</td>
</tr>
<tr>
<td>2009</td>
<td>14,983</td>
<td>769</td>
<td>5,13</td>
</tr>
<tr>
<td>TOTAL</td>
<td>52,944</td>
<td>2,384</td>
<td>4,50</td>
</tr>
</tbody>
</table>

EDT: Extrarenal depuration techniques

**PHARMACOLOGICAL CHARACTERISTICS OF MICAFUNGIN**

Micafungin is a semi-synthetic cyclical derivative of a natural compound (FR901379) produced by the fungus Coleophoma empetri. 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. 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. It has a high molecular weight (1,292.26 Da). It is more than 99% protein bound. It is metabolised in the liver, spleen and kidneys, but not in the central nervous system. 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. 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.

A study based on time-kill curves showed that micafungin has an essentially fungicide activity. 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. Some experiments have shown that the increased dose of micafungin leads to a reduction in mortality in animal models of candidiasis and aspergillosis. 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. 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.
Micafungin has been used for the treatment of peritonitis due to *Candida parapsilosis* in a female patient undergoing veno-venous haemodialysis\(^2\). 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
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.

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