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## Mini Review

## Echinocandins and Continuous Renal Replacement Therapies: The Role of Adsorption

### Introduction

The following reviews [1,2], about continuous renal replacement therapies (CRRT) and echinocandins conclude that the membranes do not significantly adsorb these antifungals.

The first review [1], that evaluates several articles [3-7], concludes that the elimination of echinocandins due to adsorption to membrane surfaces is not likely to be clinically relevant, once the concentration in steady state equilibrium is reached. They point out that 20% is lost with the first dose but that it is not relevant, at least it is not important, for anidulafungin and caspofungin because these drugs are prescribed with loading dose to achieve steady state balance on the first day. On the other hand, it indicates that in the case of micafungin, its loss could be relevant due to the lack of loading dose. This drug loss could occur mainly on the first day of TCRR or after filter replacement. A new filter has a greater adsorptive capacity and even more if the filter membranes have a high adsorptive capacity and the ultrafiltrate flows are high. It is also unknown whether repeated coagulation of the filter could affect the fungicidal activity of these antifungals. Finally, there are some limitations of these studies regarding the small size of the sample and the heterogeneity of the studied population, as well as a lack of standardization and validation of the determinations to obtain the concentrations of the echinocandins, so that it requires caution in order to evaluate the results of the studies.

The second review [2], evaluates two of the articles already included in the previous review [6,7], and concludes that micafungin can be administered in critically ill patients undergoing TCRR without the need to modify the doses or the recommended intervals. Regarding the different studies selected in both reviews (Table 1), some considerations can be added:

### Caspofungin

In the study of Weiler et al. [3], two types of deparative treatment were used in 14 patients. On the one hand, patients who were not at risk of bleeding ( $n = 7$ ) underwent hemofiltration (HFC) at doses of about 35 mL / kg / h (effluent) using a polysulfone membrane of 0.7 m<sup>2</sup> and a flow of blood of 180 mL / min, with enoxaparin as the anticoagulation of the circuit. On the other hand, patients who were at risk of bleeding ( $n = 7$ ) underwent continuous haemodialysis (HDC) at doses of about 30 mL / kg / h (effluent) using a polysulfone membrane of 1.8 m<sup>2</sup> and a regional anticoagulation of the circuit with citrate. Blood samples were taken from the arterial line at 1, 2, 4, 8, 12 and 24 hours after the initiation of caspofungin infusion. Samples were also taken at the inflow and outflow of the hemofilter (Cin - Cout) at 1 and 24 hours. In addition, samples of the effluent were also taken. However, caspofungin concentrations were only measured in 8 patients out of the 14 included in the study. In the effluent only 0.33% of the drug was found, so that its sieving coefficient (S) was 0.0033, which means that caspofungin is not eliminated by the effluent. Nevertheless, the concentrations obtained at the inflow and outflow of the hemofilter (Cin - Cout) were not detailed, and instead, authors report that the median clearance was 61 mL / h in the HFC group and 5.5 mL / h in the HDC group, with a width range of 10,712.2 mL / h (178 mL / min) and 1,550.5 mL / h (26 mL / min), for HFC and HDC, respectively. So that some patients treated with HFC could have undergone a caspofungin clearance of 178 mL / min. This article specifically details the change of filters per patient and day, and it is recorded that in 6 patients, 3 of the HFC group and 3 of the HDC group, on the day of caspofungin measurement 2 filters were used in those 24 hours, and that in 1 patient of the HFC group, up to 3 filters were used in those 24 hours in which caspofungin was measured. Unfortunately, the article does not show the caspofungin concentrations of each patient, only the average, so that it cannot be inferred that there is a relationship between repeated filter changes and the lower caspofungin concentrations. Also, in statistical terms, it is questionable the use of these medians of clearance of 61 mL / h and 5.5 mL / h, as an average of the

**Table 1:** Results from different studies.

Study	Weiler (3)	Leitner (4)	Hirata (7)	Aguilar (8)
Number of patients	14	10	4	12
Membrane	a) Polysulfone 0.7 m <sup>2</sup> b) Polysulfone 1.8 m <sup>2</sup>	Polysulfone 1.2 m <sup>2</sup>	Polymethylmethacrylate	Polysulfone 1.4 m <sup>2</sup>
CRRT type	a) Hemofiltration b) Continuous haemodialysis	Hemofiltration	Hemodiafiltration	Hemodiafiltration
Dose (mL/Kg/h)	a) 35 b) 30	17	-	25-30
Blood flow (mL/min)	180	160-180	< 100	160-180
Echinocandin type	Caspofungin	Anidulafungin	Micafungin	Anidulafungin
Effluent drug concentrations	0.33%	0%	-	0%

clearance of caspofungin, taking into account the ranges they found (10,712.2 mL / h and 1,550.5 mL / h).

### Anidulafungin

Leitner and colleagues [4], studied 10 patients undergoing HFC. The prescribed dose was about 17 mL / kg / h using a polysulfone membrane of 1.2 m<sup>2</sup> and a blood flow of 160–180 mL / min. A loading dose of 200 mg of anidulafungin was administered on the first day and continued with 100 mg / day. Arterial and venous blood samples were taken before and after starting the anidulafungin infusion, and at 2, 4, 6, 8 and 24 hours after the antifungal infusion. In addition, samples of the effluent were also taken. No anidulafungin was observed in the effluent, but a difference of 20% was detected in the area under the curve (AUC) values between arterial and venous blood. This difference, according to the authors, is due to a process of adsorption of the membrane and decreases with time; maximum at two hours when almost reaches 20% and minimum at 72 hours that hardly arrives to 10%. This decreasing effect may be due to a phenomenon of membrane saturation over time. As occurred with caspofungin, important inter-individual differences were also observed in this study, so that when measuring the AUC of anidulafungin concentrations at the inflow and outflow of the filter of several patients (n<sup>o</sup>1, n<sup>o</sup>5, n<sup>o</sup>6 and n<sup>o</sup>10), the differences were more than 20%. That is, many patients could have lost more than 20% of anidulafungin, and one of them; patient n<sup>o</sup> 6 would have lost 40% of the drug in the filter membrane. In addition, in statistical terms these results are also questionable, so that an average difference of AUC of 20.44 with a standard error of 19.79 would limit its validity.

The other study by Rosa and colleagues [5] only included 2 patients submitted to HFC.

### Micafungin

Kishino et al. [6], studied 4 transplanted liver patients who were treated with cellulose membranes, a material that is not commonly used in critically ill patients nowadays in occidental countries, so that the results are not applicable to our patients. Another Japanese study [7], included 4 patients undergoing hemodiafiltration (HDFC). In this study, polymethylmethacrylate membranes were used, blood flows were lower than 100 mL / min and the dialysis flow rate was

regulated between 500–1000 mL / h. The replacement rate flow was not well documented but it seems that the effluent was around 800–1300 mL / h, which would represent an effluent dose of 16 mL / Kg / h for an average weight of 65 Kg. Micafungin concentrations were evaluated in 3 of the 4 studied patients. An absence of micafungin in the effluent was confirmed and the average pre and post-filter concentrations did not vary in these 3 patients, with this type of polymethylmethacrylate membrane and this low dose of therapy.

It has been suggested that the differences found between the concentration at the inflow and outflow of the hemofilter found in Leitner study [4], could be due to a post-filter replacement dilution effect [7]. However, the difference in concentration from 18% (after 2 hours of CHF) to 9% (after 72 hours of CHF), with no changes in the replacement fluid rate, is easy to explain due to an adsorption phenomenon and saturation of the membrane over time. Moreover, in the study of Weiler [3], in the HDC group, without any fluid replacement, the differences between inflow and outflow concentrations of caspofungin, cannot be a consequence of a hemodilution, and instead, it could be explained from the adsorption of the drug by the membrane of the hemofilter.

Since adsorption is a saturable process, its influence on the elimination of a drug will depend on the frequency of filter change and the adsorption capacity of the membrane. As suggested in the review by González de Molina [1], an increase in the dose of CRRT could be accompanied by a greater effect on the adsorption of the echinocandins by the membranes of hemofilters.

In addition, it should be noted that adsorptive capacity of the filter membranes used in these studies was low. Membranes with more adsorption capacity like polyacrylonitrile could theoretically adsorb major amount of echinocandins. Unfortunately, these polyacrylonitrile membranes were not analysed in the studies included in the reviews [1,2], so that we cannot extrapolate the results of these studies and their conclusions if polyacrylonitrile membranes are used, regarding the adsorption of the echinocandins.

A recent study [8], in critically ill patients undergoing HDF, analyses the concentrations of anidulafungin administered with a loading dose of 200 mg / day and a maintenance dose of 100 mg / day. In this study, 1.4 m<sup>2</sup> polysulfone membranes were

used, which were changed daily. The prescribed dose was 25–30 mL / Kg / h, blood flows rates of 160–180 mL / min and the circuit was anticoagulated with sodium heparin for activated partial thromboplastin times of 35–45 seconds. Blood samples for measuring plasma anidulafungin concentrations were taken at the third day of treatment (steady state) of both the arterial and venous lines, as well as the effluent. Authors did not find any drug in the effluent, but they did detect differences in the arterial and venous concentrations of the hemofilter, finding the return ones superior to the arterial ones. The authors attribute this phenomenon to the hemoconcentration that occurs just post-filter, before being affected by the post-filter replacement. The authors of the study exclude the possibility of adsorption of the drug by the polysulfone membrane and resolved that therapeutic levels of anidulafungin were achieved in all the samples analysed. Recently, they [9] have also studied caspofungin with polysulfone membranes obtaining similar results [10].

To conclude, even though the reviews [1,2], conclude that echinocandins are not likely to be significantly eliminated by adsorption in patients undergoing CRRT, there is not enough data to be conclusive [10]. In a very recent article [11] these authors have observed that the licensed regimen of caspofungin is insufficient to achieve the PK/PD targets in critically ill patients on haemodiafiltration [11]. It is necessary to design studies with polyacrylonitrile membranes with more adsorption capacity, and also to analyse higher effluent doses and the effect of frequent filter changes.

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