DOES CONTINUOUS VENOVENOUS HAEMODIALYSIS PERFORMED WITH HIGH CUT-OFF MEMBRANE (CVVHD-HCM) AFFECT INTRAVENOUS MICAFUNGIN THERAPY IN CRITICALLY ILL SEPTIC PATIENTS?

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Background

Background: Micafungin (**MCF**) has shown poor removal by continuous renal replacement therapy (CRRT); however, it is not known whether candins can be removed by CVVHD-HCM. In critically ill patients with septic shock CVVHD-HCM have a potential benefit because it has a high cut-off membrane that purifies substances with molecular weight up to 45 kDa, including pro-inflammatory cytokines.

Aims

To explore the pharmacokinetics of MCF in patients dialyzed with CVVHD-HCM.

Methods

- This study, approved for the local Ethical Committee, was performed in 9 critically ill patients (5 liver transplants, 2 sepsis, 1 pancreatitis and 1 valvular substitution). All of them had a concomitant acute kidney injury. In all patients, APACHE II, SOFA and Candida score were calculated.
-The study was performed after at least 3 days of micafungin therapy (steady state) at the established doses of 100 mg/day, given intravenously for treatment or prophylaxis of fungal infection and before beginning the study, while patients were receiving continuous renal replacement therapy (CRRT).
- On the day of the study, a new session of CVVHD-HCM was started. The dialyser was placed one hour before the administration of the corresponding dose of micafungin provided for by the physicians in charge of patient care in the Intensive Care Unit. The samples for the analysis of micafungin in blood were performed at the scheduled times: Immediately before beginning the administration of the dose of the drug (trough) (t_0) at the end of the infusion (peak) (t_1) and then at 4, 12 and 24 hours after the peak time. The blood samples were taken in duplicate from the circuit bloodlines at the input and output ports of the dialysis filter. Dialysis effluent samples were taken at the same times. Only two patients did not have the samples collected at all the above times (see results). In patients with diuresis, 24-hour urine volume was taken and aliquots were separated to determine MCF.
- MCF determinations (HPLC) were realised in the Pharmacy Department of the Hospital del Mar (Barcelona) under the management of Dr. S. Grau. The detection and quantitation limits for plasma where 0.05-0.2 mg/L. Accuracy varies from 92.0% to 111.2% in determinations performed on the same day for plasma, and between 92.7% and 113.5% for water, with the level of variability in both fluids being 10% (Personal communication by Dr. Grau).
- CVVHD-HCM was performed using polyarylethersulfone hemofilters, a membrane with a large pore size that allows a high cut-off point (Septex®, Baxter). Blood flow used was 250 ml/min. Patients mean dialysis dose was (25.3 ml/Kg/h ±7.9 SD).
- This study was funded by a research grant from Astellas, Spain.

Results

- Median age of patients was 53.6 (range 28-80) years. General characteristics and concomitant diseases of the patients are showed in table 1 and 2 respectively.
- Median and ranges of the following scores were: SOFA (10/3-20); APACHE II (18/10-26) and Candida score (4/2-5).
- Data of the CVVHD-HCM in each patient are shown on table 3.
- In all patients, at any time of the study, MCF concentrations at pre-filter and post-filter ports were almost similar (table 4). MCF levels in the effluent were usually ≤ 0.2 mg/L (table 5).
- Clearance of MCF through the filter calculated using estimated plasma flow and differences among in-let and out-let concentrations of MCF was always null.
- The mean (±SD) of maximal concentration of MCF at t_0 and t_1 were 5.2±3.6 mg/L and 15.5±7.6 mg/L respectively. Mean $AUC_{0\text{-}24h}$ were similar when calculated using either pre (189.4±107.4 mg*h/L) or post-filter ports serum samples.
- The mean elimination half-life ($t_{1/2}$) was18.1±4.7 h.

Table 1.- Patient general characteristics

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8	PATIENT 9
Age	50	50	28	68	66	45	30	80	66
Gender	Male	Male	Male	Female	Male	Male	Female	Female	Female
Weight (kg)	200	85	55	66	71	100	60	63	78
Height (cm)	175	175	168	163	163	180	164	149	166
Date of admission to the ICU	5-12-2014	17-12-2014	18-1-2015	5-6-2015	7-6-2015	8-7-2015	11-7-2015	27-7-2015	9-9-2015
Reason for admission	Sepsis / ARDS	Pancreatitis	Liver transplant	Severe sepsis	Liver transplant	Liver transplant	Liver transplant	Prosthesis Valve	Liver transplant
Glasgow	7	11	12	4	12	13	14	10	12
SOFA	11	3	20	18	13	6	8	7	10
APACHE	17	19	20	26	22	15	10	24	18
HD Start Date	18-12-2014	27-12-2014	5-2-2015	16-6-2015	17-6-2015	23-7-2015	21-7-2015	7-8-2015	12-9-2015
MICA Start Date	15-12-2014	22-12-2014	30-1-2015	6-6-2015	12-5-2015	16-7-2015	17-7-2015	1-8-2015	9-9-2015
Candida Score	4	3	4	5	4	2	3	3	4
Diuresis 24 h (ml)	Anuria	(2300)	Anuria	Anuria	Anuria	(2000)	Anuria	Anuria	Anuria

Table 2.- Concomitant diseases present at ICU

DISEASE	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Respiratory	ARDS VM-associated pneumonia	ARDS	ARDS	ARDS Aspergilllosis	ARDS			ARDS VM-associated pneumonia	Pulmonary sarcoidosis
Neoplastic					HepatoCa.				
Infectious	Septic shock SBP Pneumonia UTI by candida	Tracheo-bronchitis by E.coli + Pseudomona	Hepatitis B. PBE Record of malaria	Biliary origin septic shock Candida in BAS and urine. Resp. infection by aspergillus	HCV infection Abdominal sepsis	Hepatitis B	Hepatitis A	Pneumonia	
Endocrine/Metabolic	Morbid obesity Subclinical hypothyroidism			Diabetes mellitus type 2	Diabetes mellitus type 2			Hypothyroidism Diabetes mellitus type 2	
Cardiovascular	Haemodynamic failure	HBP AMI March-2014		Haemodynamic failure			Right femoral pseudo-aneurysm rupture	Mitral DL Severe AS Severe PHT (Prosthesis M-Ao-T) Cardiac tamponade	
Digestive or hepatic	Cirrhosis Acute on chronic failure	Grade E pancreatitis	HBV fulminant hepatitis	Liver transplant (February 2015) Acute liver failure in transplant ADH	Liver cirrhosis HCV + hepatoCa	HBV fulminant hepatitis Liver transplant	HAV fulminant hepatitis Liver transplant		Primary biliary cirrhosis Liver transplant
Renal Genitourinary	ATN	ATN	Type 1 HRS	ATN	ATN	ATN	ATN	ATN on CKD	Type 1 HRS
Neurological or psychiatric	Hypercapnic encephalopathy	Alcohol withdrawal syndrome		Metabolic encephalopathy		Epilepsy Metabolic encephalopathy	Hepatic encephalopathy	Lacunar infarct	Depression

Table 3.- Micafungina dose and continuous haemodialysis data

Patient	1	2	3	4	5	6	7	8	9
HD Start Date	18-12-2014	27-12-2014	5-2-2015	16-6-2015	17-6-2015	23-7-2015	21-7-2015	7-8-2015	12-9-2015
MICA Start Date	15-12-2014	22-12-2014	30-1-2015	6-6-2015	12-5-2015	16-7-2015	17-7-2015	1-8-2015	9-9-2015
Daily dose MICAFUNGIN (mg/kg)	0.500	1.176	1.818	1.515	1.408	1.000	1.666	1.587	1.282
Vascular access*	Jugular 20 cm	Femoral 20 cm	Femoral 20 cm	Femoral 20 cm	Jugular 20 cm	Femoral 20 cm	Femoral 20 cm	Femoral 20 cm	Femoral 20 cm
Blood Flow (ml/min)	250	250	250	250	250	250	250	250	200
Anticoagulation	NO	Heparin	Heparin	NO	Heparin	Heparin	NO	Heparin	NO
Volume of dialysis fluid (ml/h)	2000	1500	2000	1500	2000	1800	2000	1800	2000
Dialysis Dose (ml/Kg/h)	10	17	36	23	28	18	33	28	25
Hourly extraction (ml)	80	0	100	180	160	0	140	50	130
Estimated Global Balance (ml/24h)	840	1203	1425	-1834	-2187	-820	-1003	1312	-2170

Table 4.- Pre and post-filter Micafungina concentrations

Patient	Trough Pre-filter	Trough Post-filter	Peak (1h) Pre-filter	Peak (1h) Post-filter	4 h Pre-filter	4 h Post-filter	12 h Pre-filter	12 h Post-filter	24 h Pre-filter	24 h Post-filter
1	0.6	0.6	5.2	5	2.9	2.9	2.3	2.2	1.3	1.3
2	1.2	1.1	5.9	6.1	4.1	3.9	2.5	2.5	1.2	1.4
3	7.4	6.8	23.6	24	17.2	18.3				
4	3.3	3.8	14.8	15.2	9.6	10.5	7.1	7.9	5.1	4.5
5	8.6	9.8	25.2	28.1	18.1	18.6	13.4	13.2	8.1	8.3
6	1.5	1.7	15.5	15.9	9.8	10.5	6.6	6.1	4	4
7	9.9	8.9	24	23.5	17.4	16.9	11.2	11.3	6.4	6.6
8	8.9	8.6	22	21	16	15.3	11.3	11.9	8.9	8.7
9	5.3	5.3	14	14.5	10.5	10	7.8	7.7	5.8	5.8
Mean ± SD (mg/L)	5.19± 3.65	5.18±3.56	16.69±7.6	17.03±7.94	11.73±5.77	11.88±5.86	7.77±4.06	7.85±4.15	5.10±2.84	5.07±2.82

Trough, before the iv administration of micafungin.
Peak, after the infusion in one hour.
4, 12 and 24h, hours post-peak.
There are no statistically significant differences between the pre-and post-filter concentrations of micafungin at any of the extraction times.

Table 5.- Effluent Micafungina concentrations

Patient	1	2	3	4	5	6	7	8	9
T-EFL	<0.2	NA	0.20	0.40	<0.2	<0.2	0.40	<0.2	<0.2
P-EFL	<0.2	NA	0.50	0.70	0.70	0.20	0.40	0.30	0.30
P4-EFL	<0.2	NA	0.30	0.50	0.40	<0.2	0.20	0.20	<0.2
P12-EFL	<0.2	NA		0.20	0.20	<0.2	<0.2	<0.2	<0.2
P24-EFL	<0.2	NA		<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Urine	Anuria	<0.2	Anuria	Anuria	Anuria	<0.2	Anuria	Anuria	Anuria

Discussion

- The indication for the administration of micafungin was therapeutic in two cases with invasive candidiasis (patients 1 and 4) and prophylactic in the remaining seven.
- The hourly ultrafiltrate volume was conditioned by each patient's haemodynamic situation, and was agreed to in all cases with the intensivist directly in charge of the patient. In general, the hourly extraction in each patient was low. In the 7 patients in whom it was performed, the range oscillated from 50 to 189 ml/hour. In two patients that maintained diuresis (2000 and 2300 ml on the day of the study), no ultrafiltration was performed, and the remaining patients were anuric.
- The concentrations of micafungin at the haemodialyser input and output are provided in table 4. they are practically superimposable at input and at output. The presence of micafungin in urine was detected in the two patients that maintained diuresis, albeit below quantifiable limits. As a consequence of the data pertaining to the concentrations of micafungin in plasma and in urine, it is impossible to calculate creatinine clearance through the dialyser, which may be regarded as zero. Neither does it seem plausible that a significant absorptive deposit of the drug occurred on the dialyser membrane.
- The minimum and maximum median concentrations of micafungin at time 0 (t_0), determined at the time of infusion (t_1) were, respectively: 5.30 mg/L (P75 8.75) and 15.5 mg/L (P75 23.8). The drug's median half-life $t_{1/2}$ 18.12h (P75 17.05). Moreover, the median of the area under the curve (AUC) of micafungin in the population studied was 185.7 mg/L*h (maximum and minimum values 337.2 and 57.5 mg/L*h, respectively).

CONCLUSIONS

Use of high cut-off point membranes, at least those manufactured with polyarylethersulfone (Septex, Baxter) do not dialyse micafungin and therefore no drug dose titration is required.

DOI: 10.3252/pso.eu.53era.2016