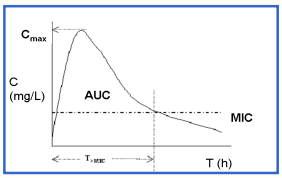
PKP 015

OPTIMAL DOSE REGIMEN OF ANTIBIOTICS AGAINST METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* IN CRITICALLY ILL PATIENTS UNDERGOING CONTINUOUS VENOVENOUS HEMODIAFILTRATION

[1]Carcelero E, [1,7]Soy D, [2,7]Guerrero L, [3,7]Castro P, [4,7]Poch E, [5,7]Fernández J, [6,7]Badia JR, [3,7]Nicolás JM.
[1]Pharmacy Service. [2]Research Lab CELLEX. [3] Medical ICU. [4]Nephrology ICU. [5]Liver ICU. [6]Respiratory ICU.
[7]IDIBAPS (Institut d'Investigacions Biomèdiques Agustí Pi Sunyer. Hosp. Clinic Barcelona. University of Barcelona.

Objetive

To evaluate the pharmacokinetics (PK) of vancomycin (VAN), linezolid (LNZ) and daptomycin (DAP) in critically ill patients undergoing continuous venovenous hemodiafiltration (CVVHDF) to optimize antibiotic dose regimens.



Patients and methods

- Prospective, one-year PK study in ICU patients undergoing CVVHDF and treated with VAN (N=10), LNZ (N=2) or DAP (N=2).
- Data collected: Patients demographics; dosage, CVVHDF characteristics, blood samples: pre-dose and several times post-dose.
- Drug concentrations were analyzed by high performance liquid chromatography – ultraviolet detection (HLPC/UV).
- CVVHDF characteristics: dialysate flow rate 0.7-1.5 L/h; ultrafiltration flow rate 0.7-2 L/h; blood flow rate 140-200 mL/min.
- PK parameters of antibiotics were determined by non-compartmental analysis: $t_{1/2}$: elimination half-life; $AUC_{0-\tau}$: area under the concentration-time curve during a dosing interval; CL_{tot}: total clearance; V_{ss}: apparent volume of distribution; CL_{CVVHDF}: vancomycin clearance by CVVHDF. Other measures: **S:** sieving coefficient; X_{CVVHDF}: total amount of vancomycin eliminated by CVVHDF.
- Optimal PK/PD indices (AUC_{0-24}/MIC) (from literature): VAN > 400; LNZ > 100; DAP > 600

Results

Vancomycin

N (M/F)	10 (8/2)
Age (y) [mean; range]	59.9 [24 - 77]
Weight (Kg) [mean; range]	73.2 [60- 90]
APACHE II score [mean ± SD]	21.9 ± 5.5
SOFA score [mean ± SD]	13.6 ± 2.7
Dose regimen (mg/kg)	15
AUC pre-filter (mg·h/L)	100 - 200
$t_{1/2}$ (h) [mean ± SD]	18.2 ± 8.5
V_{ss} (L; L/kg) [mean ± SD]	129.7 ± 64.8; (1.7± 0.8)
S [mean ± ED]	0.93 ± 0.18
CL_{CVVHDF} (L/h) [mean ± SD]	1.90 ± 0.3 (41.4 ± 12.1% CL_{tot})
CL_{tot} (L/h) [mean ± SD]	5.2 ± 1.9
$X_{CVVHDF\ (24H)}$ (mg) [mean ± SD]	401 ± 161.6

Table 1: Pharmacokinetic parameters of vancomycin in patients submitted to CVVHDF.

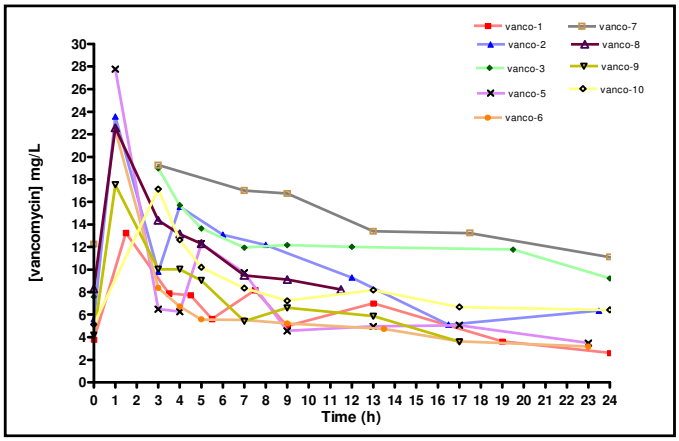


Fig. 1: Plot of pre-filter vancomycin serum concentrations against time after dose (N = 9). ID#4 (vanco-4) died 4h after recruitment (not shown). X-axis: time (hours); y-axis: vancomycin serum concentrations in mg/L.

Linezolid

pre-filter	Patient #1	Patient #2	NRF*
AUC_{0-12} (mg·h/L)	74.6	131.4	89.7± 31
$t_{1/2}$ (h)	7.4	4.9	5 -7
V_{ss} (L/kg)	0.73	0.53	0.5-0.7
CL_{CVVHDF} (L/h)	1.8 **	2.3 ‡	CL_r: 2.59
CL_{tot} (L/h)	5.3	3.6	7.4
$X_{CVVHDF\ (24H)}$ (mg)	154.8	282.9	-
CL_{nr} (L/h)	3.5	1.4	-
C_{max} (mg/L)	16.5	21.2	15.1 ± 2.5
C_{min} (mg/L)	5.2	5.6	3.7 ± 2.4
S	0.82	0.74	-

Table 2: Pharmacokinetic parameters of linezolid in patients submitted to CVVHDF compared to patients with normal renal function (NRF)*(from literature). **represents 33.9% of CL_{tot}; ‡represents 63.9% of CL_{tot}.

Daptomycin

pre-filter	Patient #1	Patient #2	NRF*
AUC_{0-24} (mg·h/L)	379.9	468.6	700-1000 (8-10 mg/kg)
$t_{1/2}$ (h)	12.6	28.7	7 -11
V_{ss} (L/kg)	0.23	0.17	0.1
CL_{CVVHDF} (L/h)	0.6 **	0.3 ‡	CL_r: 0.47
CL_{tot} (L/h)	1.28	1.1	0.5-0.7
$X_{CVVHDF\ (24H)}$ (mg)	312.8	310.3	-
CL_{nr} (L/h)	0.6	0.75	0.13
C_{max} (mg/L)	42.9	92.0	106.2 (SD 20) (8 mg/kg)
C_{min} (mg/L)	13.2 (at 24h)	26.2 (at 24h)	10.3 (at 24h) (8 mg/kg)
S	0.28	0.18	-

Table 3: Pharmacokinetic parameters of daptomycin in patients submitted to CVVHDF compared to patients with normal renal function (NRF)* (from literature). ** represents 46.8% of CL_{tot}; ‡ represents 27.3% of CL_{tot}.

Conclusions

- **Vancomycin** was significantly removed by CVVHDF with effluent rates of 2 L/h (40 ± 16.2% of the given dose). A dose > 15 mg/kg/day appears to be necessary to optimize the PK/PD target. TDM is strongly recommended.
- **Linezolid** was partially removed by CVVHDF. Plasma concentrations and PK/PD indexes related to effectiveness were appropriate for susceptible microorganisms (MIC ≤ 2 mg/L). It could be suitable to increase dosage in bacteria with higher MIC values to linezolid in order to optimize the AUC_{0-24}/MIC ratio.
- A significant percentage of **daptomycin** dose was cleared during 24h in our patients. A dose of 8 mg/kg/48h seems insufficient to achieve the PK/PD target. Higher DAP doses would be needed (10-12 mg/kg/48h).

Authors have no conflict of interest in this study.