eP005

The effect of ECMO in critically ill patients on meropenem PK: a matched cohort study

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Introduction

Extracorporeal membrane oxygenation (ECMO) is being increasingly used in adult patients with acute severe cardiorespiratory failure as a supportive therapy. While ECMO sustains life, stabilises physiology and allows time for pathology to be treated, little is known about the independent effects of ECMO on pharmacokinetics. ECMO is thought to further complicate the pharmacokinetic (PK) alterations seen during critical illness. Gram negative bacteria are responsible for significant proportions of these infections acquired during ECMO and meropenem is used as an empirical or targeted broad-spectrum antibiotic in this setting. In the presence of ECMO, changes in meropenem PK are likely although no data presently exists to guide dosing.

This open-label, descriptive PK study aimed to describe meropenem PK during ECMO using critically ill patients with sepsis and not receiving ECMO as controls.

Materials and Methods

Ethics approval was obtained from the local ethics committee and informed consent was obtained from study participants or surrogate decision makers as applicable. Serial blood sampling for meropenem was performed in patients receiving ECMO and a sample of critically ill patients with sepsis not receiving ECMO. Meropenem plasma concentrations were determined using validated chromatography. The concentration-time data for meropenem in plasma were fitted using a non-linear mixed-effects modeling approach (NONMEM version 7.1, Globomax LLC, Hanover, USA). Based on the final covariate model, we chose to simulate various scenarios to highlight the importance of patient and ECMO and hybrid renal replacement therapy (RRT) treatment specific characteristics.

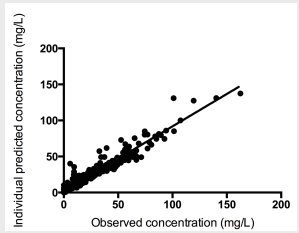
Results

Eleven ECMO [veno-venous (VV) ECMO, n=6; veno-arterial (VA) ECMO, n=5] patients in 10 non-ECMO critically ill controls without renal dysfunction were included. The indications for ECMO included pneumonia, septic shock (n=7); cardiogenic shock (n=2); sickle cell crisis (n=1); primary graft dysfunction post lung transplant (n=1). The demographic and clinical data are summarised in Table 1.

Table 1: Characteristics of included patients	Controls (n=10)	ECMO (n=11)	*P* value
Male/Female	7/3	4/7	0.1
Age (years)	56(48–63)	30 (16–47)	0.007
Total body weight (kg)	77 (75–85)	70 (69–80)	0.11
Height (cm)	174 (170–183)	170 (165–175)	0.11
Mechanical ventilation	10	11	0.47
Type of ECMO (VA/VV)	-	5/6	-
Day 1 SOFA score	3.5 (2–5)	13 (8-17)	0.001
Serum creatinine (μmol/L)	77 (55–109)	82 (70–178)	0.45
Creatinine clearance (mL/min)	102 (81–160)	69 (62–150)	0.18
Extended daily diafiltration (Yes /No)	0/10	5/6	0.03

Results continued

Param-eter	Model	Bootstrap		
	Mean	Mean	95 % CI	
Fixed effects				
CL (L/h)	16.0	16.0	2.1	20.6
Vc (L)	9.8	9.8	7.6	12.6
Vp (L)	14.9	15.2	13.2	17.2
Q (L/h)	40.9	42.8	29.7	61.7
CL_{ECMO}	0.42	0.45	0.30	0.65
CL_{RRT}	0.62	0.87	0.32	2.1
CL_{CrCL}	0.14	0.28	0.11	1.09
$Vc_{,ECMO}$	2.30	2.32	1.47	3.38
Random effects BSV (% CV)				
Cl (L/h)	33.8	31.4	19.8	43.1
Vc (L)	47.5	46.4	33.5	62.0
Vp (L)	16.6	13.5	0.1	27.1
Random error				
RUV (% CV)	24.9	23.4	17.5	29.5
RUV (mg/L)	0.53	0.71	0.31	1.69



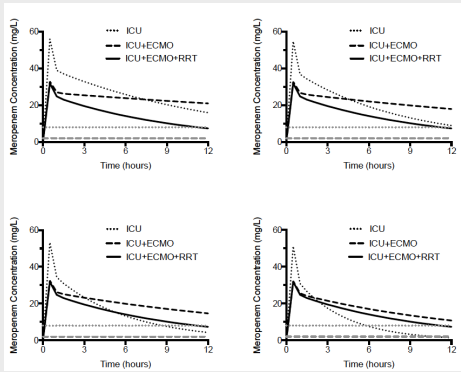


Figure 1: (Top) Goodness of fit plot
Figure 2: (Bottom) Various simulations highlighting PK effects of ECMO and RRT

Conclusions

ECMO patients had significantly higher volume of distribution (0.53±0.17 vs. 0.32±0.07, p<0.05) and lower clearance compared to controls (7.3±5.6 vs. 15.9±6.8 L/h p<0.05). Variability in meropenem clearance was correlated with creatinine clearance or the presence of RRT, while patient weight correlated with the volume of distribution of the central compartment. In ECMO patients, while a usual meropenem target minimum inhibitory concentration (MIC) of > 2mg/L in all patients, a more aggressive target of >8mg/L (4x MIC) aimed at less susceptible microorganisms was maintained only in 8(6 RRT) /11 patients.

Given that ECMO patients exhibit high PK variability, standard meropenem dosing (1g IV q8h) may not always result in optimal drug concentrations, especially when targeting higher MICs. Clinicians need to consider the presence of ECMO, renal function or RRT and microbiological characteristics when choosing doses for patients.

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