Meropenem Dosage Optimization in Critically Ill Patients Based on a Population Pharmacokinetic Approach

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Introduction

Meropenem (MEM) is commonly used to treat serious infections and displays wide variability in plasma concentrations after administration of the same dose in critically ill patients due to factors that affect MEM volume of distribution (V) and clearance (CL) (e.g. edema, sepsis, kidney failure). These alterations could lead to not achieve the pharmacokinetic/pharmacodinamic (PK/PD) target with the consequent failure of antibacterial therapy.

Objective

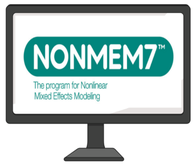
The aim of this study was to describe MEM PK parameters in critically ill patients in order to establish safe and effective initial dosing regimens adapted to patients characteristics.

Methods

78 critically ill patients

Blood sampling: predose, 1, 3 and 6h post-dose

HPLC-UV/Vis plasma concentrations determination



POP-PK model and MC simulations

Conclusion

This study demonstrates the wide variability in MEM PK and enhances the need to include therapeutic drug monitoring as part of stewardships interventions in critically ill patients to maximize bacteriological and clinical responses.

Results

Table 1. Demographic and clinical characteristics of critically ill patients included for model development and validation.

Characteristic	Value
Sex (male/female) (n)	45/33
MEM plasma concentrations (n)	229
Age (years)[a]	47 ± 17
Weight (kg)[a]	67 ± 13.8
Height (m)[b]	1.62 (1-1.9)
BMI (kg/m^2)[a]	25.5 ± 5.4
Serum creatinine (mg/dL)[a]	0.97 ± 0.83
CLCr (mL/min/1.73 m^2)[a]	102.97 ± 47.1
MEM dose (mg/day)[b]	3000 (500-6000)

BMI, body mass index; CLCr, creatinine clearance in mL/min/1.73 m^2 calculated by CKD-EPI formula. [a] Presented as mean ± SD [b] Presented as median (range)

Figure 1. Monte Carlo simulations and PTA (50% fT>MIC) for MEM under different conditions. Dashed line indicates a PTA of 90%.

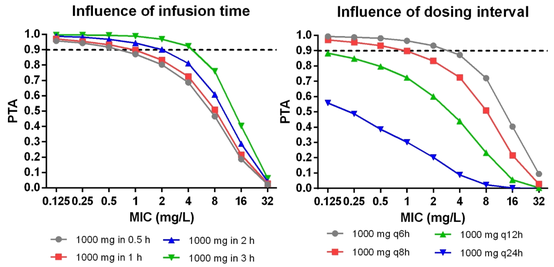


Table 2. Pharmacokinetic parameters, interindividual variability, residual error values and bootstrap results (n=1000) obtained for the final one compartment open model of MEM in critically ill patients.

Pharmacokinetic model	Parameter	Mean	RSE (%)	Shrinkage (%)	Bootstrap		
					Median	Percentiles 2.5%	Percentiles 97.5%
CL (L/h)= θ_1 × (CLCr/102)	θ_1	11.9	8	-	11.93	10.01	14.06
V (L)	θ_2	25.2	11	-	24.92	20.17	30.16
IIV - CL (CV%)	ω^2_{CL}	56.2	8	7	55.7	46.56	64.77
IIV - V (CV%)	ω^2_V	47	18	31	46.6	20.75	62.09
Residual variability (µg/mL)	σ	3.53	42	28	3.44	1.49	4.93

CL, clearance; V, volume of distribution; IIV, interindividual variability; θ, fixed parameters; ω y σ, random parameters; CLCr, creatinine clearance in mL/min/1.73m^2 calculated by CKD-EPI formula; RSE, relative standard error.

Table 3. MEM dosing recommendations for critically ill patients to achieve a PK/PD target of %t>CMI of 50% or 100%.

CLCr (mL/min/1.73 m^2)	%t > CMI 50%	%t > CMI 100%
20	1000 mg e24h in 0.5 h 500 mg e12h in 0.5 h 500 mg e8h in 0.5 h	500 mg e12h in 0.5 h 500 mg e6h in 0.5h
40	500 mg e12h in 2h 1000 mg e12h in 0.5 h 500 mg e8h in 0.5 h	1000 mg e8h in 2h 1500 mg e8h in 0.5h 500 mg e6h in 0.5h
60	1000 mg e12h in 3 h 1500 mg e12h in 2 h 500 mg e8h in 0.5 h	1000 mg e6h in 3h 1500 mg e6h in 2h
80	2000 mg e12h in 3 h 500 mg e8h in 3 h 1000 mg e8h in 1 h	* Continuous infusion is highly reccomended
100	500 mg e8h in 3 h 1000 mg e8h in 2 h	
120	1000 mg e8h in 3 h 1500 mg e8h in 2 h 500 mg e6h in 2 h	
140	1000 mg e8h in 3 h 500 mg e6h in 3 h	
160	1500 mg e8h in 3 h 500 mg e6h in 3 h	
180	500 mg e6h in 3 h 1500 mg e6h in 2 h	

Dosing regimens are given as dose, dosing interval and infusion time

Figure 2. VPC plot for MEM plasma concentrations versus time after dose.