Population pharmacokinetics of meropenem in febrile neutropenic patients in Korea.

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Introduction

- Meropenem had been given as 1.5 gram/day (0.5 g every 8 hours) regimen, the lowest approved dose partially for healthcare cost containment in Korea without in-depth consideration of clinical efficacy.
- Even in the case of critically ill patients *i.e.*, neutropenia, this tendency for prescribing the 'minimum recommended dose' has not been altered.
- Therefore we carried out this study to explore the population PK of meropenem given as 0.5 gram every 8 hours in febrile neutropenic patients.

Objectives

To evaluate the "1.5 gram/day" regimen with pharmacometric tools

- Estimate population PK parameters
- Estimate a PD endpoint (Time above MIC, TAM) based upon MIC data from clinically isolated P.aeruginosa

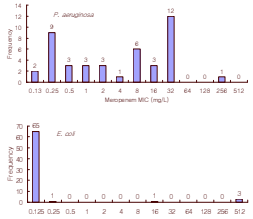
Subjects & Methods

1.Fifty seven neutropenic patients who were admitted to the hematologic malignancy unit at the Catholic Hematopoietic Stem Cell Transplantation (HSCT) center in Seoul, Korea.

2.*Ethics Review and Consent*

Written informed consent obtained in a form approved by the IRB of St. Mary's Hospital

Characteristics	Median (Range)
Age (y)	36 (17-68)
Number	57 (female 27 / male 30)
Height (cm)	162.6 (141-190)
Weight (kg)	61.4 (45-95.8)
Underlying Disease*	AML 36; ALL14; MDS 4; others 4
CL_{Cr} (ml/min)	121 (26.4-152.2)



3. MIC's of clinically isolated *P. aeruginosa* and *E. coli* strains, which were from neutropenic patients from the same unit from 2000 to 2003, were used to estimate the TAM.

4. *Meropenem administration and Blood sampling*

Dosage regimen - 0.5 g of meropenem (10 min infusion) every 8 hours

Venous blood withdrawn 2-3 h (for peak) and 5-6 h (for trough) after the injection at steady state.

5. *Plasma Meropenem Assay*

HPLC (based on the method reported by Ip *et al.,* 1998)

- LOQ 0.5 mg/L
- Linear from 0.5 to 50 mg/L of standard solution.

6. *Population PK model development :* NONMEM (version 5.1.1).

- PREDPP subroutines ADVAN1 TRANS2 used
- Structural model : 1-compartment, first order elimination

  $CL_i = CL_{pop} \times e^{\eta CL}$, $Vd_i = Vd_{pop} \times e^{\eta Vd}$

  η_{CL} and η_{Vd} : independent random-error variables (means 0 and variance of ω_{CL}^2 and ω_{Vd}^2, respectively)
- Residual error: $C_{ij} = C_{ij(pred)} (1+ \varepsilon_{prop\ ij})$

  C_{ij}: observed jth concentration in the ith individual;

  $C_{ij(pred)}$: the concentration predicted for the ith individual
- FOCE method with interaction used
- Bootstrap method: More than 1,000 successfully minimized re-samples to obtain 95% confidence intervals (CI) for parameter estimates

7. *Simulation of Concentrations*

- A Monte-Carlo clinical trial simulation experiment using Pharsight Trial Simulator® (Pharsight Corporation, version 2.1.2, Mountain View, CA, USA)
- MICs : simple discrete proportions, just as observed in the MIC test histograms, were used instead of assuming any distribution model.
- a total of 1,000 virtual patients' data were generated for differing dosage regimens and pathogens.
- Simulated TAM (Time above MIC) : assumption of 92% of total concentration unbound (Dreetz et al., 1996)

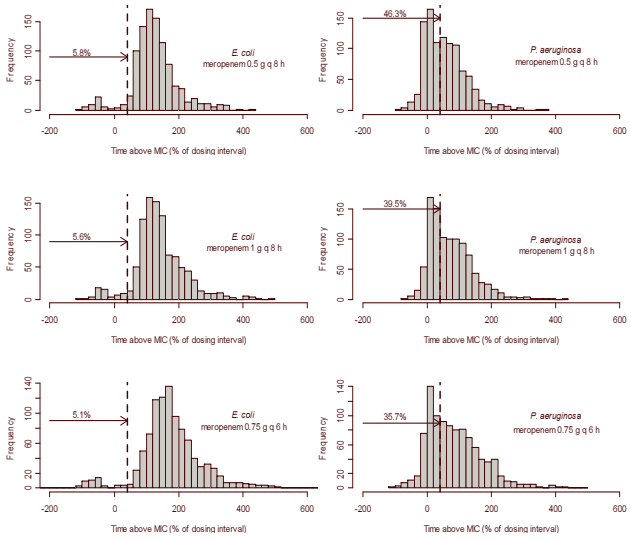
$$TAM = \frac{\ln\left(\frac{C_{SSpeak}}{MIC}\right)}{\frac{CL}{Vd}}$$

Results

Population PK

Parameter	Meaning	Symbol	Mean and 95% C.I.¶
CL (L/h)	$CL_{pop} = \theta_1 \times (CL_{Cr}{}^{\dagger}/120)$	θ_1	9.7 (7.56-11.82)
	$CL_i = CL_{pop} \times e^{\eta CL}$	ω_{CL}	0.73 (0.66-0.79)
Vd (L)	$V_{pop} = \theta_2 \times$ (Body weight‡/61)	Θ_2	14.6 (11.08-18.1)
	$Vd_i = Vd_{pop} \times e^{\eta Vd}$	ω_{Vd}	0.54 (0.53-0.86)
Correlation	Correlation coefficient between (CL and Vd)	-	0.998 (0.88-1)
Half-life (hr)	$t_{1/2}$ *	-	1.04 (0.94-1.14)
Residual Error	C_{ij} (Observed Conc.) = $C_{ij(pred)} \times (1+ \varepsilon_{prop})$	σ_{prop}	0.298 (0.00-0.31)

Simulated TAM's



Frequency distribution of TAM (Time above MIC) as percentage of the dosing interval) for P. aeruginosa and E. coli isolates when meropenem was given 0.5 g q 8h, 1 g q 8h and 0.75 g q 6h in 1000 simulated patients. A TAM greater than 40% of the dosing interval was chosen as a cut-off point for clinical efficacy. Dotted lines indicate 40% of the dosing interval and percentage values above the arrows indicate the proportion of patients with TAM shorter than 40% of the dosing interval.

Discussion

Meropenem 1 g q 8h in neutropenic Korean patients is expected to be more effective than a 0.5 g q 8h regimen which was implemented without pharmacodynamic consideration of highly resistant strains.

For P. aeruginosa, we need a comprehensive re-evaluation of treatment strategies including aminoglycoside combination, meropenem monotherapy with higher dosage or consideration of other susceptible antibiotics.

References

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Dreetz M, Hamacher J, Eller J, et al. Serum bactericidal activities and comparative pharmacokinetics of meropenem and imipenem-cilastatin. Antimicrob Agents Chemother 1996; 40:105-9.