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

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Dosage regimen - 0.5 g of meropenem (10 min infusion) every 8 hours Venous blood withdrawn 2-3 h (for peak) and 5-6 h (for trough) after the injection at steady state.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.

- PREDPP subroutines ADVAN1 TRANS2 used
- Structural model: 1-compartment, first order elimination
  CL = CLpop × exp(θ1 × propij)
  Vd = Vdpop × exp(θ2 × propij)
  θ1 and θ2: Independent random-error variables (means 0 and variance of 0.75 and 0.75, respectively)
  Residual error: Cij = Cij(pred) × (1 + εij)
  Cij: observed jth concentration in the ith individual;
  Cij(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)

Results

Population PK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Symbol</th>
<th>Mean and 95% C.I.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>$CL_{pop} \times e^{\theta_1 \times \text{propij}}$</td>
<td>$\theta_1$</td>
<td>10.7 (8.6-12.8)</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>$Vd_{pop} \times e^{\theta_2 \times \text{propij}}$</td>
<td>$\theta_2$</td>
<td>5.73 (4.66-7.07)</td>
</tr>
</tbody>
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Correlation
- Correlation coefficient between (CL and Vd) - 0.998 (0.88-1)

Half-life (h)
- $t_{1/2}^{\text{CL}}$ - 1.04 (0.94-1.14)

Residual Error
- $C_i (\text{Observed Conc.}) = C_{\text{pred},i} (1 + \varepsilon_{ij})$
- $\sigma_{\text{prop}}$ = 0.298 (0.20-0.31)

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 1,000 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