Effect of infusion time on the pharmacodynamic profiling of Meropenem in critically ill patients with *Pseudomonas aeruginosa* infections

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Abstract PHC003

BACKGROUND:

- **Severe infections in critically ill patients due to *P. aeruginosa* require timely and adequate antibiotic treatment.**
- **The pharmacokinetic (PK) profile in ICU patients is too variable to optimize therapeutic outcome by using the standard dosages.**
- **The minimum inhibitory concentration (MIC) becomes a surrogate of the pharmacodynamics (PD) of the combining infecting bacteria and drug.**
- **Regarding carbapenems (meropenem: MEP), the PK/PD index to be optimized is the time for which the free serum drug concentration exceeds the MIC: $fT_{SS>MIC}$**
- **Monte Carlo simulations facilitate to theoretically forecast the probability of PK/PD target attainment (PTA).**

AIM:

This analysis evaluates through Monte Carlo simulations, the appropriateness of meropenem (MEP) extended IV infusions (EI) in critically ill patients with *P. aeruginosa* infections.

METHODS:

- **A 5000 patient Monte Carlo simulations, based on previous population PK data from ICU patients[1] and creatinine clearance (CLcr): 80 mL/min, 40 mL/min and 20 mL/min, were performed to predict steady-state concentration (C^{SS})-time profiles (NONMEM v.6).**
- **Typical adult doses of MEP (MEP 1g IV q6h-q8h-q12h) were simulated as 0.5h, 1h, 2h and 3h extended IV infusions (EI).**
- **A range of MICs was studied, S: ≤ 2 mg/L, I: 4 mg/L and R: > 8 mg/L, according to the EUCAST cut-off[2] for *P. aeruginosa* to MEP.**
- **The likelihood of target attainment (PTA_{50}: $fT^{SS}_{>MIC}$ > 50%), was calculated (SPlus 6.1) for each EI while keeping the interdose interval of 6h, 8h or 12h. A PTA_{50} value > 90% was considered satisfactory.**

RESULTS:

- **In patients with CLcr around 80 mL/min:**
  - **High doses of MEP: 1g IV for 30 min/6h were needed to reach PTA_{50} > 90%) for MICs ≤ 2 mg/L. For higher MICs, even this dose was clearly inadequate. (Fig.1)**
    i.e: MIC = 4 mg/L PTA_{50} : 76.5%
    MIC = 8 mg/L PTA_{50} : 38.8%
  - **PTA_{50} markedly increased by using EI up to 3 h. Considering 1g IV of MEP/6h and a MIC value of 4 mg/L:**

PTA_{50}:	85.2%	94.8%	100%	
EI:	1 h	2 h	3 h	(Fig.1; middle panel)

  - **When using EI, lower MEP doses (1g IV/8h) could be prescribed without loss of efficacy for MIC values ≤ 2 mg/L.**

PTA_{50}:	89.7%	95.1%	99.1%	
EI:	1 h	2 h	3 h	(Fig.2; left panel)

- **PTA_{50} remained above 90% whilst Clcr = 40 mL/min, for the usual regimens (1g/6h or 8h 30 min) and MICs ≤ 2 mg/L. (Fig.3)**
- **When Clcr = 20 mL/min, MEP 1g IV/12h reached PTA_{50} values slightly below or above 90% for MIC = 4 mg/L, despite infusion length. (Fig.4)**

Fig. 1: CLcr = 80 mL/min and MEP 1g IV/6h for EI of:
30 min: purple solid line 1 h: orange dashed line
2 h: green dashed line 3 h: red dashed line

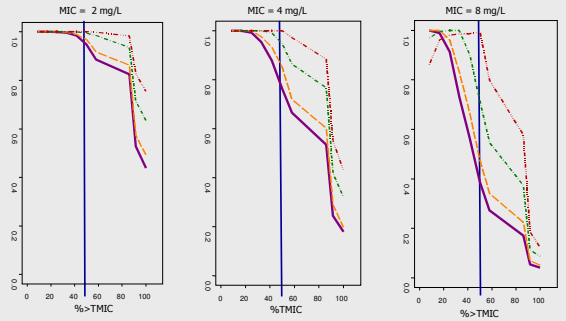
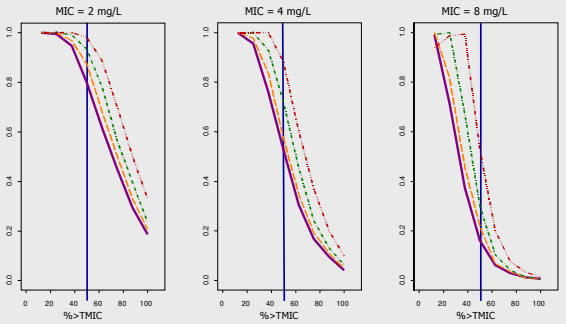
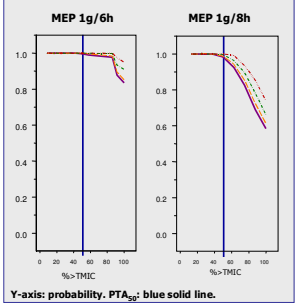


Fig. 2: CLcr = 80 mL/min and MEP 1g IV/8h IV



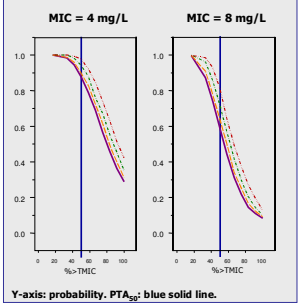
Y-axis: probability. PTA_{50}: blue solid line.

Fig. 3: CLcr = 40 mL/min and MIC ≤ 2 mg/L



Y-axis: probability. PTA_{50}: blue solid line.

Fig. 4: CLcr = 20 mL/min and MEP 1g/12h IV



Y-axis: probability. PTA_{50}: blue solid line.

CONCLUSIONS:

- **The probability of attaining PTA_{50} for a given MIC rises as long as the infusion time increases.**
- **The length of infusion has less impact on PTA_{50} in patients with moderate/severe renal impairment.**
- **MEP administered as an extended infusion of 3h might increase the likelihood of microbiological eradication and clinical outcome in ICU patients and high MICs for *P. aeruginosa*.**

1. Li Ch, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. J Clin Pharmacol 2006; 46: 1171-78.
2. European Committee Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for MICs interpretation & zone diameters. EUCAST Clinical Breakpoint Table v.1.3 2011-01-05. Version1.3, Jan 2011. [http://www.eucast.org/clinical_breakpoints/] Accessed July 2011.

Author has no conflict of interest in this study.