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: \( t_{SS>\text{MIC}} \).
- 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 patients and creatinine clearance (CLcr): 80 mL/min, 40 mL/min and 20 mL/min, were performed to predict steady-state concentration (CSS)-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 for P. aeruginosa to MEP.
- The likelihood of target attainment (PTA_50: \( t_{SS>\text{MIC}} > 50\% \)), 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)
    \[ \text{MIC} = 4 \text{ mg/L, PTA}_50 = 76.5\% \]
    \[ \text{MIC} = 8 \text{ mg/L, PTA}_50 = 38.8\% \]
  - 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:
    \( \text{PTA}_50: 85.2\% 94.8\% 100\% \)
    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.
    \( \text{PTA}_50: 89.7\% 95.1\% 99.1\% \)
    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)

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.


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