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Individual target pharmacokinetic/pharmacodynamic attainment rates among meropenem-treated patients admitted to the ICU with hospital-acquired pneumonia

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Objectives: Critical illness reduces β-lactam pharmacokinetic/pharmacodynamic (PK/PD) attainment. We sought to quantify PK/PD attainment in patients with hospital-acquired pneumonia.

Methods: Meropenem plasma PK data ($n = 70$ patients) were modelled, PK/PD attainment rates were calculated for empirical and definitive targets, and between-patient variability was quantified [as a coefficient of variation (CV%)].

Results: Attainment of 100% $T_{>4\times MIC}$ was variable for both empirical (CV% = 92) and directed (CV% = 33%) treatment.

Conclusions: Individualization is required to achieve suggested PK/PD targets in critically ill patients.

Introduction

Broad-spectrum β-lactam antibiotics such as meropenem are frequently used in hospital-acquired pneumonia (HAP) treatment.[1] Pharmacokinetic (PK) variability caused by augmented renal function, renal replacement therapy and/or expanded intravascular volume can lead to insufficient pharmacodynamic (PD) exposures.[2–4] Importantly, pathogens infecting critically ill patients in the ICU are more likely to have higher meropenem MICs versus non-ICU patients.[5,6]

A suggested target for plasma concentrations of β-lactams is 100% $T_{>1\times MIC}$ in ICU patients.[7] However, 100% $T_{>4\times MIC}$ is considered to be an optimal PK/PD target,[8] and attainment of $T_{>4\times MIC}$ has been associated with improved clinical outcomes.[9] However, whether population-based β-lactam dosing consistently yields sufficient PK/PD for ICU patients is unclear.[10–14]

We evaluated meropenem PK/PD attainment in plasma among HAP patients admitted to our ICU and characterized the inter-individual variability in target PK/PD attainment.

Materials and methods

We analysed meropenem concentrations within plasma samples collected as part of the Successful Clinical Response In Pneumonia Therapy (SCRIPT) study (https://script.northwestern.edu). Critically ill patients with HAP admitted to the Medical ICU at Northwestern Memorial

Hospital (Chicago, IL, USA) were enrolled between 30 June 2018 and 1 March 2021. Plasma samples salvaged from clinical care were stored per protocol prior to −80°C. Pathogens were cultured from deep (i.e. bronchoalveolar lavage) respiratory sampling and identified using standard microbiological methods.

Total meropenem was quantified using the Agilent 1260 Infinity Binary LC system paired with the Agilent 6420 Triple Quadrupole MS system. A reversed phase Poroshell (Agilent) C18 column (100 mm × 3.0 mm × 2.7 μm) was used. Mobile phases A and B were 0.1% formic acid in water and LC/MS-grade acetonitrile, respectively. Transitions (*m/z*) for meropenem were: quantitation 384.1 → 68.2, qualification 384.1 → 141.0; ceftazidime (*m/z*: 274.1 → 80.2) served as an internal standard. The assay was linear from 0.125 to 100 μg/mL ($R^2 = 0.999$). Accuracy (inter-day: 93.95%; intra-day: 96.45%) and precision [inter-day coefficient of variation (CV%): 3.9%; intra-day CV%: 0.9%] met FDA requirements for bioanalytical method validation.[15]

A non-parametric population PK model was developed with the non-parametric adaptive grid (NPAG) algorithm using the Pmetrics package (version 1.9.7) for R (version 4.0.0).[16] Given the sparse nature of sampling, only a one-compartment model was evaluated. Calculated CL_{CR},[17] serum creatinine, total body weight, height, age, gender and renal replacement therapy were evaluated as covariates. Model selection was performed using visual inspection of goodness-of-fit plots and minimization of the Akaike information criterion (AIC) among competing models. Patients with meropenem concentrations below the limit of quantification (BLQ) were excluded from the PK/PD analysis.

Posterior meropenem PK profiles (predictions generated every 0.2 h) were generated for the first 24 h. PK/PD target attainment was evaluated for 100% $T_{>1\times MIC}$ and 100% $T_{>4\times MIC}$ for empirical (i.e. pathogen-specific MICs determined by the microbiology laboratory) and directed [i.e. the breakpoint MIC for *Pseudomonas aeruginosa* of 2 mg/L[18]] treatment. Between-patient variability in target attainment was quantified using CV%.

Ethics

Institutional Review Boards (IRBs) approved the study (IRB ID# STU00204868 at Northwestern University and IRB ID# 20058 at Midwestern University).

Results

A total of 83 blood samples were available from 70 (35.7% female) patients, as shown in Figure S1, available as Supplementary data at *JAC* Online. A stability analysis indicated that degradation under study protocol conditions would be <<15% (Figure S2). Twelve patients had BLQ concentrations. Table 1 summarizes demographic and clinical characteristics. The median first 24 h meropenem dose was 4 g/day (IQR 3–4 g/day).

A one-compartment multiplicative residual error model best fitted the data. The final model included 22 support points (Table S1). The mean estimates for volume of distribution (*V*) and CL were 34.07 L and 5.3 L/h, respectively. Population and individual predicted versus observed goodness-of-fit plots are shown in Figure S3.

Within our cohort, PK/PD data were available (i.e. non-missing) for 15 patients who were treated empirically and 43 patients who were treated definitively. For those treated empirically, pathogen MICs ranged from 0.25 to 32 mg/L. Detected pathogens, their MICs and meropenem doses are summarized in Table S2.

Individual target attainments for those treated empirically are illustrated in Figure 1. PK/PD variation, quantified as CV%, was 54%–92% with empirical treatment and 26%–33% for directed treatment considering targets of 100% $T_{>1\times MIC}$ and $T_{>4\times MIC}$, respectively.

Table 1. Demographic data and clinical characteristics

Demographics	*N*	Median	Range
Age (years)	70	65.5	25–83
TBW (kg)	70	75.2	46.7–166.4
HT (cm)	70	168	147–188
BMI (kg/m^2)	70	25.9	16.6–51.2
SCr (mg/dL)	70	0.92	0.20–4.92
CL_{CR} (mL/min)	70	82.6	14.3–418.5
RRT	6		
Sex			
Male	45		
Female	25		

N, number of patients; TBW, total body weight; HT, height; BSA, body surface area; SCr, serum creatinine; RRT, renal replacement therapy (includes intermittent haemodialysis and continuous renal replacement).

Discussion

We found considerable between-patient variability in meropenem PK/PD target attainment. Most patients received our institutionally recommended dosing of 1 g every 8 h infused over 3 h (or adjusted for kidney function). Considering a PK/PD goal of 100% $T_{>1\times MIC}$, we found that 47% of patients treated empirically and 35% of patients receiving directed therapy failed to achieve this goal. If the more stringent target of 100% $T_{>4\times MIC}$ is applied, 53% of patients treated empirically and 70% of patients receiving directed therapy would fail to achieve this goal. While population approaches increase the likelihood of target attainment, individualization is clearly required for many critically ill patients.

In the absence of individualized dosing, a significant number of HAP patients are at risk of experiencing inadequate PK/PD based on our findings. Roberts *et al.*[12] found that increasing $T_{>MIC}$ significantly improved the survival after adjusting for clinical covariates. Scharf *et al.*[13] found that time to infection resolution was improved for patients who achieved 100% free-drug $T_{>1\times MIC}$ versus those who did not. Gijsen *et al.*[14] also found low attainment for 1× and 4× MIC (46% versus 11%, respectively). Penetration into the site of infection (i.e. alveolar fluid) is also important. Lodise *et al.*[19] found high variability for meropenem epithelial lining fluid penetration and that even the highest approved doses of meropenem may not achieve PK/PD targets. Thus, individualized dosing appears to be necessary to ensure target attainment in ICU patients.

Sparse sampling constrained our ability to identify a more complex model. However, identification of a one- versus a two-compartment model does not impact the assessment of $T_{>MIC}$ greatly. While sample degradation is a potential concern, the results of our stability analysis indicate that drug loss should be minimal under the protocolized sample handling in SCRIPT. A limitation to our study was that we are not yet able to link PK/PD to clinical outcomes. Future studies will investigate the effect of suboptimal target attainment on clinical outcomes.

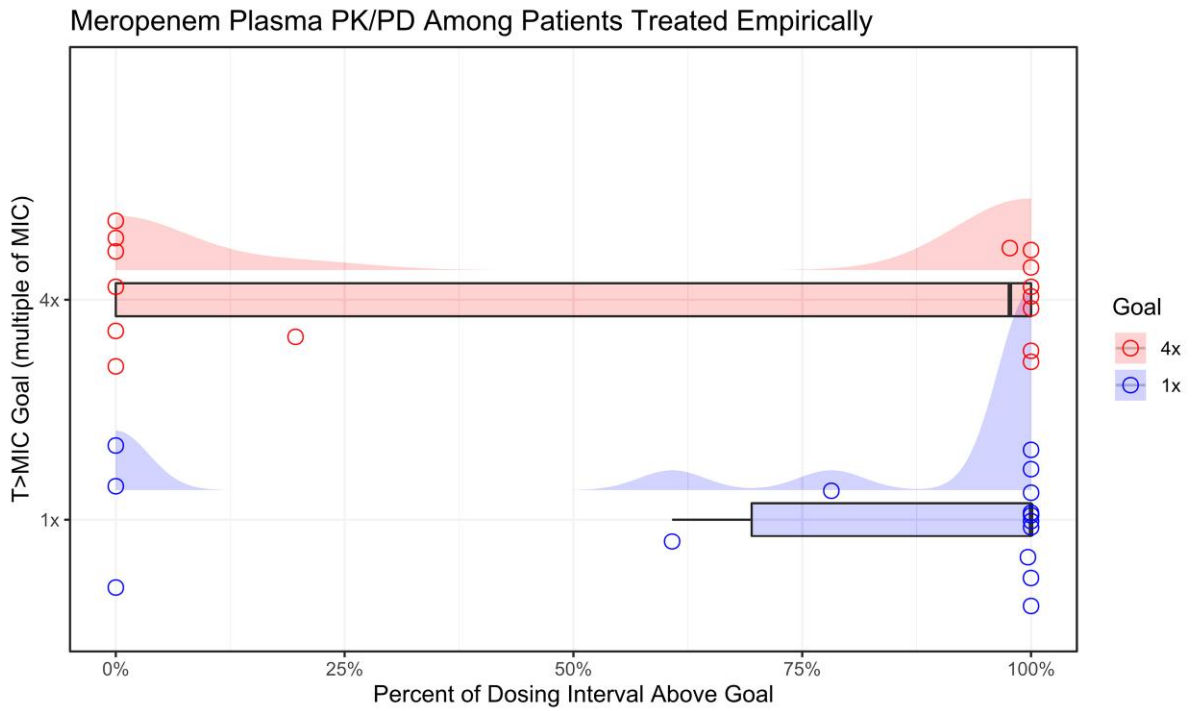

Figure 1. Individual meropenem plasma PK/PD attainment among patients treated for HAP. PK/PD target attainment stratified by target (blue = $T_{>1\times MIC}$, red = $T_{>4\times MIC}$) among patients treated empirically. Individual observations (open circles) are jittered to increase visual clarity where values overlap. The distribution of observed PK/PD ratios is shown in box plots, with overlaid density (half-eye) plots demonstrating the range and density of PK/PD ratios in the sample.

In conclusion, meropenem-treated HAP patients are at risk for inadequate PK/PD in spite of extended-infusion dosing due to patient-specific variability in PK. Thus, an individualized approach to treatment is needed to achieve suggested PK/PD targets.

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Transparency declarations

None to declare.

Supplementary data

Figures S1 to S3 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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