Clinical Pharmacokinetics (2024) 63:1573–1583
https://doi.org/10.1007/s40262-024-01436-6

ORIGINAL RESEARCH ARTICLE

Impact of Continuous Infusion Meropenem PK/PD Target Attainment on C-Reactive Protein Dynamics in Critically Ill Patients With Documented Gram-Negative Hospital-Acquired or Ventilator-Associated Pneumonia

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Accepted: 30 September 2024 / Published online: 25 October 2024

Abstract

Background and Objective Population pharmacokinetic/pharmacodynamic (PK/PD) modelling of antibiotics including C-reactive protein (C-RP) dynamics could be helpful in predicting the efficacy of antimicrobials. We developed a PK/PD model for assessing the impact of continuous infusion (CI) meropenem PK/PD target attainment on C-RP dynamics in critically ill patients with documented Gram-negative hospital- (HAP) or ventilator-acquired pneumonia (VAP).

Methods Patients were grouped according to the type of antibiotic treatment received [meropenem monotherapy; meropenem plus empirical anti-MRSA (methicillin-resistant *Staphylococcus aureus*) therapy; meropenem in combination with another anti–Gram-negative active agent; meropenem plus a targeted anti-MRSA therapy]. A one-compartment population PK model of CI meropenem was developed by including all patients. A full C-RP production inhibition model was developed for fitting the PD data by including only patients receiving meropenem monotherapy or meropenem plus empirical anti-MRSA therapy. Monte Carlo simulations explored the relationship between the type of PK/PD target attainment of CI meropenem, defined as optimal (steady-state plasma concentration [C_{ss}] to minimum inhibitory concentration [MIC] ratio = 4–8), quasi-optimal (C_{ss}/MIC = 1–4) and sub-optimal (C_{ss}/MIC < 1) and the magnitude of C-RP production inhibition over time.

Results A total of 64 patients providing 211 meropenem concentrations were included in the PK analysis, whereas 47 patients providing 328 C-RP data were included in the PD model. Simulations showed that optimal PK/PD target attainment was associated with the highest and most rapid C-RP production inhibition (44% and 56% at days 2 and 4, respectively). Conversely, sub-optimal PK/PD target attainment was shown to be almost ineffective (< 5% at day 4 and < 10% at day 10).

Conclusion Our PK/PD model predicted that attaining optimal PK/PD target with CI meropenem may grant prompt and intense C-RP decrease among critically ill patients receiving targeted monotherapy for Gram-negative HAP/VAP, thus anticipating efficacy.

1 Introduction

Pneumonia, bloodstream infections and urinary tract infections are the most frequent health-care associated bacterial infections arising in critically ill patients due to a mix of invasive device positioning, underlying comorbidities and/or immunosuppression [1]. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) may have prevalence rates of 24.7–34% [2, 3], with high crude mortality rates [4]. Gram-negative bacteria are the most frequent pathogens, accounting for 77.9% of isolates [5], and may cause difficult-to-treat infections, especially when being multidrug-resistant (MDR).

In the clinical scenario of HAP/VAP, meropenem is a first-line treatment when dealing with critically ill patients being at high risk of infections caused by *Pseudomonas aeruginosa* and/or by extended-spectrum β-lactamases (ESBL)-producing *Enterobacterales* [6]. According to treatment guidelines, in the presence of risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) such as prior isolation of MRSA, recent hospitalization or recent exposure to parenteral antibiotics, an anti-MRSA agent should be added [6].

Extended author information available on the last page of the article

Key Points

The relationship between meropenem exposure and C-reactive protein decrease in critically ill patients with hospital- or ventilator-acquired pneumonia may be accurately explored using population pharmacokinetic/pharmacodynamic (PK/PD) modelling.

In patients treated with meropenem monotherapy or combined with an empirical anti Gram-positive antibacterial, optimal PK/PD target attainment (namely a steady-state plasma concentration [C_{ss}] to minimum inhibitory concentration [MIC] ratio of 4–8) was associated with the highest and most rapid inhibition of C-reactive protein production (44% and 56% at days 2 and 4, respectively).

Meropenem is a β-lactam antibacterial with time-dependent antibacterial activity, meaning that the time during which the concentrations are above the minimum inhibitory concentration (MIC) is the major pharmacodynamic determinant of efficacy [7]. Continuous infusion administration (CI) coupled with real-time therapeutic drug monitoring (TDM) were shown to be highly beneficial in increasing the likelihood of attaining aggressive pharmacokinetic/pharmacodynamic (PK/PD) targets with meropenem [8–10]. A recent study meta-analyzed the impact of aggressive PK/PD target attainment compared with conservative PK/PD target attainment of β-lactam among critically ill patients receiving treatment for documented Gram-negative infections [11]. It was shown that aggressive PK/PD targets (defined as a steady-state plasma concentration [C_{ss}] to MIC ratio > 4–5 or C_{ss}/MIC ratio > 4–5 and corresponding to > 100%$T_{4\text{-}5\times MIC}$) were associated with higher clinical and microbiological response rates compared with conservative ones (defined as C_{ss}/MIC ratio of 1) [11].

C-reactive protein (C-RP) is produced by the liver in the acute phase of an infectious disease mainly in response to the release of pro-inflammatory cytokines, namely interleukin (IL)-6 [12]. Onset C-RP serum levels are biomarkers of the burden of the inflammatory response in infectious diseases and effective antimicrobial treatment is expected to promote rapid and progressive decrease over time up to its complete production inhibition [13]. In patients with VAP, serum C-RP dynamics was recently shown to be a good biomarker of the efficacy of antibiotic therapy. A prospective, multicenter, observational study carried out among 37 patients with microbiologically documented VAP showed that both the C-RP dynamics and its relative changes were significantly different between survivors and non-survivors and that adequate initial antibiotic therapy was associated with faster C-RP decrease (53% vs 4% at day 4 in survivors and non-survivors; $p = 0.029$) [13]. Although achieving antibiotic exposure PK/PD targets remains key to assess efficacy of antibiotic treatments, it fails to consider various patient- and/or disease-specific factors which may modulate treatment response. Biomarkers related to the immune response to infection, such as C-RP, offer a more direct and individualized measure of the patient/host response to infection. To date, it remains unclear from a quantitative perspective how the dynamics of C-RP should be interpreted in terms of its potential application towards individualized dosing strategies.

Based on these assumptions, we developed a population PK/PD model for assessing the impact of CI meropenem PK/PD target attainment on C-RP dynamics in critically ill patients with documented Gram-negative HAP or VAP.

2 Patients and Methods

This monocentric, retrospective study was conducted at the IRCCS Azienda Ospedaliero Universitaria di Bologna, Italy, during the period December 2020 to August 2023 among critically ill patients having documented Gram-negative HAP/VAP treated with CI meropenem and undergoing real-time therapeutic drug monitoring (TDM) of meropenem. The study was approved by the Local Ethics Committee (No. 308/2021/Oss/AOUBo) on 24 May 2021. Due to the retrospective nature of this investigation, informed written consent was waived.

Meropenem treatment was always started with a loading dose of 2 g over 2 h immediately followed by an initial maintenance dose (MD) based on estimated glomerular filtration rate (eGFR), namely 1 g every 6 h (q6h) or 0.5 g q6h over 6 h for eGFR ≥60 or < 60 mL/min/1.73 m^2, respectively. Stability of 24-h CI meropenem was granted by reconstituting the aqueous solution every 6–8 h and by administering it over 6–8 h [14]. Patients underwent real-time TDM firstly after at least 24 h from starting treatment and subsequently every 48–72 h whenever feasible. Expert clinical pharmacological recommendations were simultaneously provided for a properly adjusted dosing regimen focusing on attaining an aggressive meropenem PK/PD target defined as C_{ss}/MIC ratio of 4–8 [15–17]. Meropenem concentrations were analyzed by means of a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) [18].

The following demographic and clinical data were retrieved from each patient's medical record: age, gender, weight, height, serum creatinine (S-Cr), eGFR, type and

site of infection and microbiological isolates with pathogen susceptibility data in terms of MIC. The Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) formula was used to estimate eGFR [19].

2.1 Population PK/PD Modelling

For PK model development we included all patients who received meropenem, regardless of being in mono or combination therapy. For PD model development, however, we included only patients who received meropenem alone or in combination with an empirical anti-MRSA therapy because we deemed that in the other patients C-RP production inhibition could have been affected by the targeted anti-MRSA and/or by the additional anti-Gram-negative therapy.

First, a population PK model of CI meropenem was developed by using a one-compartment model with first-order elimination from the central compartment. As CI administration made it unfeasible to estimate volume of distribution (V), V was fixed at 20 L, based on a previous model [16]. Then, a PK/PD model was developed and fitted to the individual C-RP concentrations over time. A sequential PK/PD model was built in a two-step process for preventing possible instability and biases in modelling clinical sparse data [20–23]. In order to enable faster convergence, in this second model the PK parameters were fixed to the PK estimates previously obtained. The structural base PK/PD model was an indirect turnover model with full inhibition of C-RP production as follows:

$$\frac{\mathrm{dCRP}}{\mathrm{d}t} = k_{\mathrm{in}} \times 1 - \frac{C}{C + \mathrm{IC}_{50}} - k_{\mathrm{out}} \times \mathrm{CRP}$$

$$k_{\mathrm{in}} = \mathrm{CRP}_0 \times k_{\mathrm{out}}$$

where k_{in} is the C-RP production rate; C, the meropenem steady-state concentration; k_{out}, the C-RP degradation rate; $\mathrm{C\text{-}RP}_0$, the C-RP concentration at baseline and IC_{50} is the meropenem concentration causing half-maximal C-RP production inhibition. The structure of the PK/PD model is depicted in Fig. 1.

All individual parameters were log-normally distributed. Exponential random effects were assumed to describe inter-individual variability. Correlations between random effects were tested in the variance–covariance matrix and implemented into the structural model accordingly. Additive, proportional and combined error models were tested for residual variability. The following clinical covariates were tested on the PK parameters: age, sex, weight, height, serum creatinine and eGFR. Similarly, the MIC value of the clinical isolate, type of Gram-negative microbiological isolates (*Pseudomonas aeruginosa* vs other Gram-negative pathogens) and the addition of empirical anti-MRSA therapy were tested on the PD parameters. A covariate was included in the model if reductions in the objective function value (OFV) > 3.84 points, of both the Akaike information criteria (AIC) and Bayesian information criteria (BIC), of the inter-individual variability and of the relative standard errors (RSE) of the fixed-effect parameters were observed. Population PK/PD modelling was conducted with the stochastic approximation of expectation maximization (SAEM) algorithm of Monolix 2023R1.

2.2 Model Evaluation

Model evaluations were based on the goodness-of-fit of the observed versus population- and individual-predicted concentrations, on the distribution of the weighted residuals and on the visual predictive check (VPC) plot. The VPC plot depicts the time course of the 10th, 50th and 90th percentiles of meropenem or C-RP concentrations and the corresponding 90% prediction intervals calculated from 500 Monte Carlo samples. Moreover, a non-parametric bootstrap resampling technique of 1000 patients was used to evaluate the uncertainty of all the PK and the PD parameter estimates. From the bootstrap empirical posterior distribution, the 95% confidence interval (2.5–97.5 percentiles) for the parameters was obtained. The bootstrap resampling was obtained using the "Rsmlx" package in R (R version 4.2.1).

2.3 Monte Carlo Simulations

Monte Carlo simulations from the final PK/PD model were performed with Simulix 2023R1. The developed PK/PD model was used to generate 100,000 C-RP concentration-versus-time profiles for the following CI meropenem dosages (125 mg q8h over 8 h, 500 mg q8h over 8 h, 500 mg q6h over 8 h, 1000 mg q6h over 8 h and 1500 mg q6h over 8 h)

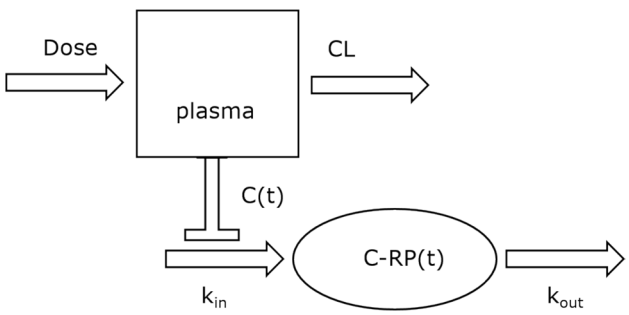

Fig. 1 Representative continuous indirect response pharmacokinetic/pharmacodynamic model, based on a one-compartment pharmacokinetic model and meropenem effect described by inhibition of C-reactive protein (C-RP) production. *CL* meropenem clearance, *C(t)* meropenem concentration, k_{in} C-RP production rate, k_{out} C-RP degradation rate

in relation to five different classes of renal function (0–30, 31–60, 61–90, 91–120 and 121–150 mL/min/1.73 m^2). Median C-RP percentage reduction from baseline was calculated against four different C_{ss}/MIC ratio ranges, namely < 1 (defined as sub-optimal), 1–4 (defined as quasi-optimal), 4–8 (defined as optimal) and > 8 (defined as supra-optimal) [24]. All plots were generated using the "ggplot2" package in R (R version 4.2.1).

3 Results

3.1 Demographics and Clinical Data

A total of 154 patients were screened, of whom 64 were definitely included in the study and divided in four groups as shown in Fig. 2. Patient demographics and clinical characteristics are summarized in Table 1. Median (IQR) age, weight, eGFR and baseline C-RP were 65.5 (57.0–74.0) years, 75.0 (65.0–85.0) kg, 70.0 (39.0–100.0) mL/min/1.73 m^2 and 15.65 (9.2–26.1) mg/dL, respectively. Median (IQR) duration of meropenem treatment, dose and C_{ss} were 9.0 (6.5–14.0) days, 2.0 (1.5–4.0) g daily by CI and 15.9 (9.8–27.6) mg/L, respectively. Overall, 47 Gram-negative clinical isolates were identified from patients included in the PD model (Table 2). Of these, the most frequent ones were *Pseudomonas aeruginosa* (13/47, 27.7%), *Klebsiella pneumoniae* (13/47, 27.7%) and *Acinetobacter baumannii* (7/47, 14.9%).

3.2 Population PK/PD Modelling

A total of 211 meropenem plasma C_{ss} were included in the PK model. A one-compartment model with first-order elimination was used as the base model, and eGFR was included as a covariate on clearance (CL) in the final population pharmacokinetic model. eGFR was a significant covariate on meropenem CL (decrease of 45.73 and 43.73 points in the OFV and AIC, respectively) as follows: CL (L/h) = $2.72 \times e^{(0.011 \times eGFR)}$. The final covariate model showed an R^2 of the observed versus predicted concentrations of 0.72 (Fig. 3A) without any visible trend of the residuals over time (Fig. 3C).

A total of 328 C-RP concentrations were included in the PD model. There were two resulting covariates significantly associated with the meropenem IC_{50} estimate, namely the MIC value of meropenem against the clinical isolate (decrease of 4.83 for the OFV and 3.93 for the AIC) and the presence of an empirical anti-MRSA therapy (decrease of 11.83 for the OFV and 9.83 for the AIC, respectively). The structural relationship between the IC_{50} and both the MIC and the presence of an anti-MRSA therapy was as follows: IC_{50} (mg/L) = $0.79 \times e^{(0.44 \times MIC)} \times e^{(2.46 \times DRUG)}$ (Table 3).

Overall, C-RP concentrations were well fitted with a good agreement between the observed and predicted data, with an R^2 of 0.77 (Fig. 3B) without any visible trend of the residuals over time (Fig. 3D).

The VPC for both the PK and PD parts of the model showed that the medians and the 10th and 90th percentiles were inside the simulated prediction intervals (Fig. 4A and B). Moreover, the PK and the PD parameters were within 95% CI of the bootstrap and close to the bootstrap median. The parameter estimates of the final model are summarized in Table 3. The structure of the final PK/PD model is reported in the electronic supplementary material (ESM).

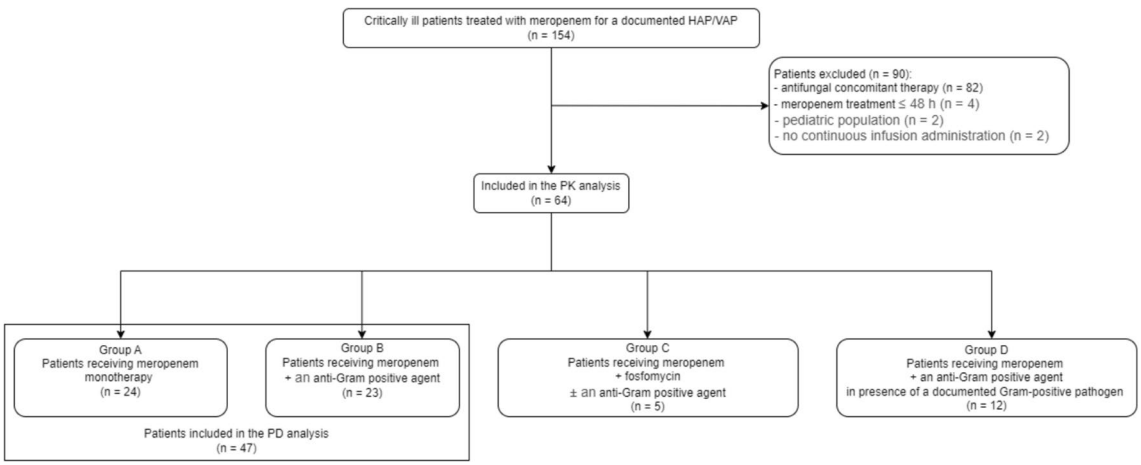

Fig. 2 Flow chart of patient inclusion and exclusion criteria and of classification into treatment groups according to the presence and type of co-administered antimicrobial. *HAP* hospital-acquired pneumonia, *PD* pharmacodynamics, *PK* pharmacokinetics, *VAP* ventilator-associated pneumonia

Table 1 Demographics and clinical characteristics ($n = 64$ patients)

Age (years)	65.5 (57.0–74.0)
Gender (M/F)	36/28 (56.25/43.75)
Height (m)	1.70 (1.68–1.75)
Weight (kg)	75.0 (65.0–85.0)
Serum creatinine (mg/dL)	0.96 (0.62–1.31)
eGFR (mL/min/1.73 m^2)	70.0 (39.0–100.0)
Meropenem treatment	
Median dose (g daily by CI)	2 (1.5–4)
Treatment duration (days)	9 (6.5–14)
N. of TDM assessment per patient	3 (2–4)
Pharmacokinetics	
Meropenem C_{ss} (mg/L)	15.9 (9.8–27.6)
Pharmacodynamics[a]	
Baseline C-RP (mg/dL)	15.7 (9.2–26.1)
C-RP (mg/dL)	11.5 (6.2–20.2)
N. of C-RP assessment per patient	8 (5–11)
Patients co-treated with anti-Gram-positive agent	23 (48.9)[a]
SOFA score	10 (6–15)
APACHE score	17 (12–20)
Use of mechanical ventilation	45 (95.7)
Use of ECMO	2 (4.3)
Presence of shock	25 (53.2)
Any surgical intervention	23 (48.9)

Data are presented as median (IQR) for continuous variables and as number (%) for dichotomous variables

CI continuous infusion, *C-RP* C-reactive protein, *Css* steady-state concentration, *ECMO* extracorporeal membrane oxygenation, *eGFR* estimated glomerular filtration rate, *TDM* therapeutic drug monitoring

[a]Statistics are calculated on the number of patients included in the pharmacodynamics analysis ($n = 47$)

Table 2 Summary of microbiological data ($n = 47$)

		MIC (min–max) ranges (mg/L)
Reason for meropenem use		
VAP	35 (74.47)	
HAP	6 (12.77)	
VAP + BSI	5 (10.64)	
HAP + BSI	1 (2.12)	
Gram-negative isolates		
Pseudomonas aeruginosa	13 (27.66)	0.12–16.00
Klebsiella pneumoniae	13 (27.66)	0.12–8.00
Acinetobacter baumannii	7 (14.89)	0.12–64.00
Enterobacter aerogenes	3 (6.38)	0.12
Serratia marcescens	3 (6.38)	0.12–8
Escherichia coli	2 (4.26)	0.12–2
Enterobacter cloacae	2 (4.26)	0.12–1
Proteus mirabilis	2 (4.26)	0.12
Klebsiella oxytoca	1 (2.13)	0.12
Enterobacter bugandensis	1 (2.12)	1
Overall MIC (mg/L)	0.25 (0.12–4.00)	0.12–64
Microbiological eradication[a]	28 (63.63)	
Clinical outcome		
Cured	29 (61.70)	
Failed	18 (38.30)	

Data are presented as median and IQR (or min-max range for MIC value) for continuous variables and as number (%) for dichotomous variables

BSI bloodstream infection, *HAP* hospital-acquired pneumonia, *MIC* minimum inhibitory concentration, *VAP* ventilator-associated pneumonia

[a]Among the 44 patients with broncho-alveolar lavage cultures in at least one subsequent assessment

3.3 Monte Carlo Simulation

Median C-RP dynamics in patients receiving CI meropenem in monotherapy and in combination with an empirical anti-MRSA therapy in relation to the type of PK/PD target attainment are shown in Fig. 5A and B, respectively.

In patients receiving only CI meropenem, optimal PK/PD target attainment was linked with the most rapid and intense C-RP reduction, namely by 40% at day 2 and by a further 15% at day 4 (overall 55% at day 4), with a total reduction of 75% at day 10. Interestingly, supra-optimal PK/PD target attainment did not improve the rapidity and the magnitude of C-RP reduction compared with optimal PK/PD target attainment (80% vs 75% at day 10; $p = 0.5036$). Quasi-optimal PK/PD target attainment was associated with less intense C-RP reductions compared with optimal PK/PD target attainment, namely by 25%, 35% and 50% at days 2, 4 and 10, respectively. Conversely, sub-optimal PK/PD target attainment had minimal impact, with C-RP decreasing by only 5% at day 4 and < 10% at day 10.

In patients receiving CI meropenem in combination with an empirical anti-MRSA therapy, supra-optimal, optimal, quasi-optimal and sub-optimal PK/PD target attainments were associated with similar trends in C-RP decreases over time to those observed in patients receiving only CI meropenem, but less intense (C-RP reduction at day 10 of 40%, 35%, 17% and 2%, respectively).

4 Discussion

In this study, we developed a population PK/PD model for assessing the impact of CI meropenem PK/PD target attainment on C-RP dynamics among critically ill patients having documented Gram-negative HAP/VAP. The findings showed that the popPK model was reliable and that promptly

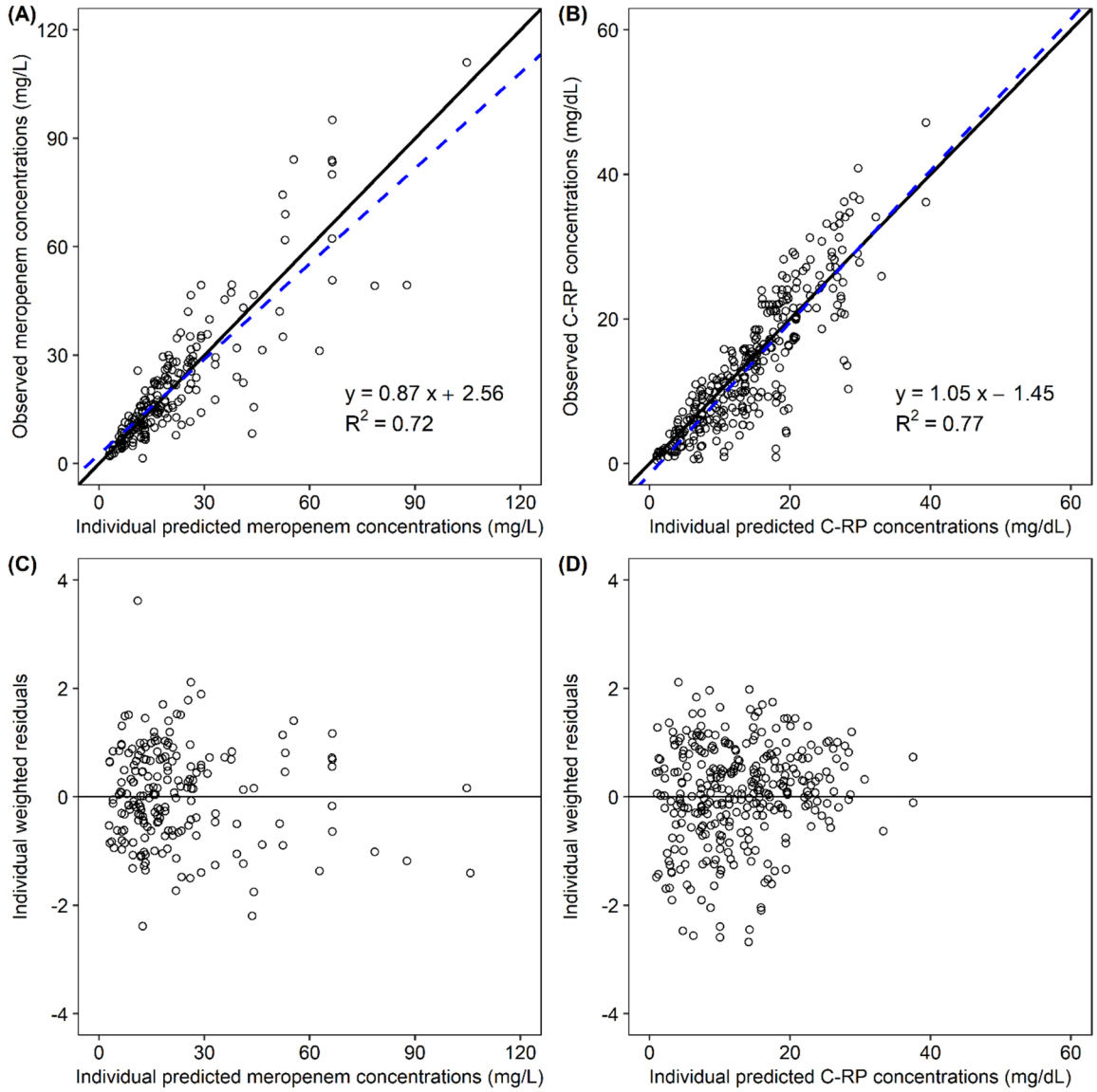

Fig. 3 Diagnostic plots for the population pharmacokinetic (left panels) and pharmacodynamic (right panels) models. Shown are observed versus individual-predicted concentrations (**A**) and individual weighted residuals (IWRES) versus individual-predicted concentrations (**C**) for meropenem in plasma, and observed versus individual-predicted concentrations (**B**) and individual weighted residuals (IWRES) versus individual-predicted concentrations (**D**) for C-reactive protein (C-RP) in plasma. The *dashed blue line* represents the line of regression

attaining a C_{ss}/MIC ratio of 4–8 with CI meropenem allowed for a very fast and intense C-RP decrease.

Looking at the popPK model, a one-compartment model adequately fitted the data, in agreement with previous studies [16, 25–27]. Estimated glomerular filtration rate was the only covariate significantly linked to meropenem CL, consistent with previous findings [16, 26, 28–30] and with meropenem being mostly renally excreted [31, 32]. The reliability of the model is supported by the low RSE% values for all of the PK parameter estimates and agreement of CL estimates scaled by eGFR with those reported in previous studies carried out among critically ill patients (4.66 L/h vs 4.20 L/h [30] for eGFR of 49 mL/min/1.73 m^2 and 7.44 L/h vs 7.27 L/h [16] for eGFR of 91.5 mL/min/1.73 m^2).

In regard to the PD model, our choice of testing a turnover response model with full inhibition of C-RP production described successfully the C-RP dynamics in our population and is in agreement with what was done in other previous studies on this topic [21, 33, 34]. However, it should not be overlooked that all of the previous studies investigating this topic assessed only the impact of antibiotic exposure on C-RP kinetics [21, 33, 34], and did

Table 3 PK/PD model parameter estimates

Parameter	Estimate (%RSE)	Bootstrap median	Bootstrap 95% CI
PK model			
Population parameters			
CL_{MER}	2.72 (16.7)	2.73	2.32–3.13
V (L)	20 (fixed)	20 (fixed)	20 (fixed)
Covariate effect			
CL_{CR} on CL_{MER}	0.011 (20.0)	0.011	0.0085–0.014
Inter-individual variability			
ω CL_{MER}	0.59 (10.4)	0.58	0.52–0.64
Residual variability			
Proportional error	0.37 (6.53)	0.36	0.33–0.41
PD model			
Population parameters			
C-RP_0 (mg/dL)	22.58 (9.55)	21.51	20.47–23.04
IC_{50} (mg/L)	0.79 (53.4)	1.02	0.38–1.32
k_{out} (h^{-1})	0.012 (27.2)	0.012	0.0097–0.014
Covariate effect			
MIC on IC_{50}	0.44 (15.9)	0.31	0.24–0.48
Group on IC_{50}	2.46 (31.9)	2.50	1.92–3.97
Inter-individual variability			
ω C-RP_0	0.51 (15.8)	0.48	0.39–0.59
ω IC_{50}	1.59 (22.5)	1.32	1.12–2.00
ω k_{out}	1.08 (21.6)	1.01	0.82–1.51
Residual variability			
Proportional error	0.35 (4.87)	0.38	0.35–0.44

CI confidence interval, CL_{CR} creatinine clearance, CL_{MER} meropenem clearance, *C-RP* C-reactive protein, $C\text{-}RP_0$ C-RP value at baseline, IC_{50} half maximal inhibitory concentration, k_{out} C-RP degradation rate, *MIC* minimum inhibitory concentration, *PD* pharmacodynamics, *PK* pharmacokinetics, *%RSE* percentage of relative standard error, *V* meropenem volume of distribution, ω standard deviation of inter-individual variability

Proportional error was estimated using: $observation = prediction \times (1 + proportionalerror)$

not take into account the pathogen's susceptibility, namely the MIC value. Indeed, this is a very important issue when dealing with a targeted therapy since the effectiveness of an antimicrobial should depend on a parameter incorporating both drug exposure and the degree of the pathogen's susceptibility, namely the PK/PD target attainment. To the best of our knowledge, ours is the first PK/PD model that, by incorporating the MIC value of the clinical isolate as a significant covariate on the antibiotic IC_{50} of C-RP production, allowed us to establish the impact of PK/PD target attainment on C-RP kinetics.

Monte Carlo simulations showed that, during CI meropenem monotherapy, attaining an early optimal C_{ss}/MIC ratio of 4–8 may grant the fastest relative C-RP decrease (55% at day 4), thus anticipating the adequacy of treatment. Conversely, attaining only a suboptimal PK/PD target of C_{ss}/MIC ratio < 1 may cause only minimal C-RP decrease (< 5% at day 4), thus anticipating treatment failure.

These findings may offer additional opportunities for supporting how to optimize the efficacy of meropenem therapy in HAP/VAP patients, and are in agreement with recent evidence reported by others. A prospective, observational study showed that among patients with documented VAP, the C-RP decreases at day 4 were of a similar extent to those predicted by our models depending on the initial antibiotic therapy being adequate or inadequate (53% in survivors vs 4% in non-survivors, $p = 0.029$) [13]. Several recent studies showed that aggressive PK/PD target attainments of β-lactams were associated with either better clinical cure and microbiological eradication of Gram-negative infections or lower resistance development to β-lactams [11, 16, 35, 36]. A recent meta-analysis assessing the impact of PK/PD target attainment on the clinical efficacy of β-lactams for the treatment of Gram-negative infections in critically ill patients showed that an aggressive PK/PD target was significantly associated with both higher clinical cure rate (OR 1.69; 95% CI 1.15–2.49) and lower risk of β-lactam resistance development (OR 0.06; 95% CI 0.01–0.29) [11].

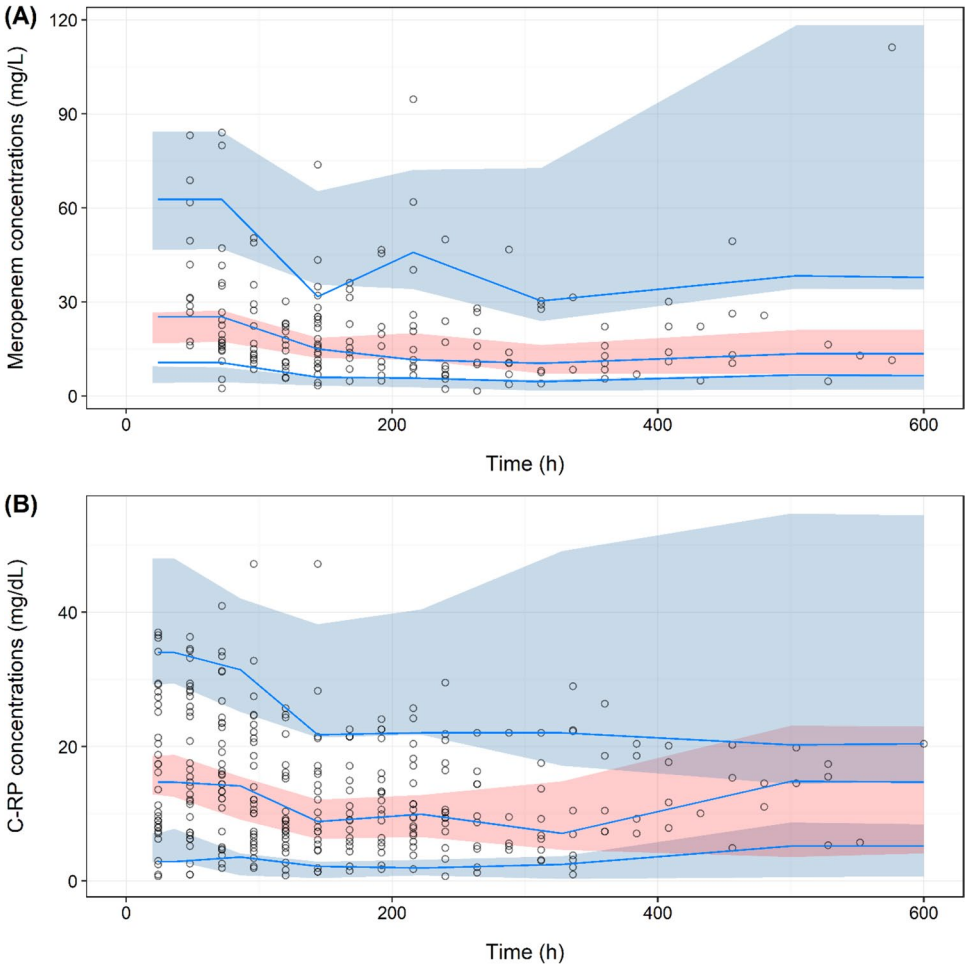

Fig. 4 Visual predictive check (VPC) for the population pharmacokinetic (**A**) and pharmacodynamic (**B**) models. *Blue lines* represent the median, 10th and 90th percentiles of the observed values; *shaded areas* are the prediction intervals for the median (*red central area*) and 10th and 90th percentiles (*light blue bottom and top areas*). *C-RP* C-reactive protein

The developed model predicting C-RP kinetics in relation to meropenem exposure could anticipate meropenem efficacy in patients with VAP. It may be expected that patients attaining optimal PK/PD target since the beginning of treatment may have a rapid C-RP decrease, namely > 50% at day 4 and > 75% at day 10, thus potentially benefiting from earlier therapy discontinuation. Shortening the duration of antimicrobial treatment to no more than 7 days is recommended by both the European and the American guidelines on VAP/HAP [37, 38]. C-RP-guided therapy was shown to be non-inferior to 7- and 14-day fixed antimicrobial therapy in terms of 30-day rate of clinical failure among patients with uncomplicated Gram-negative bacteremia [39], but further investigations are warranted in the context of more challenging clinical scenarios like those of VAP/HAP. This investigation shows the importance that attaining optimal PK/PD targets may have on C-RP decline. This is consistent with previous observations linking attainment of meropenem C_{ss}/MIC > 4.63 to favorable clinical outcomes among critically ill patients with documented Gram-negative infections [16] and of meropenem C_{ss}/MIC > 5 on both microbiological eradication and prevention of resistance development [35]. Aggressive PK/PD target attainment may be favored by CI administration and by applying TDM, provided that real-time dose adjustments and appropriate interpretation of plasma exposure in relation to patient pathophysiological conditions are ensured [40].

We acknowledge some limitations of our study. The retrospective design and the heterogenicity of the patient case-mix must be recognized. The impact of optimal PK/PD target attainment of CI meropenem on CR-P decrease was lower in patients receiving meropenem in combination with an empirical anti-MRSA therapy. This might suggest that Gram-positive related infections could have affected in some way the C-RP dynamics, even though no difference in severity score was observed between patients with and without combination therapy that might support a role of worsening clinical conditions independent of anti-MRSA agents. Finally, we recognize that also testing PK/PD models other than the turnover indirect model would have been preferable.

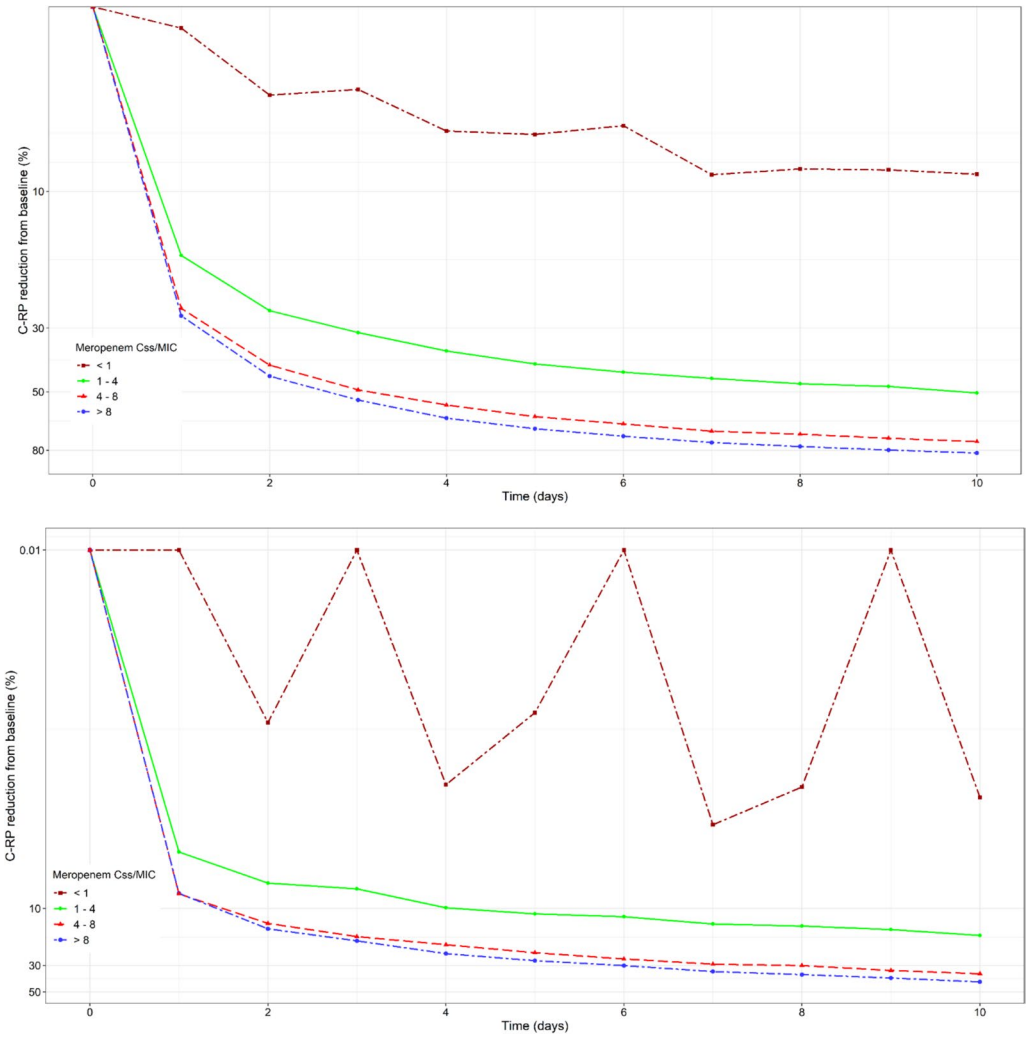

Fig. 5 Simulated median C-RP relative reductions from baseline according to different C_{ss}/MIC ratios in patients treated with meropenem monotherapy (**A**) and in those treated with meropenem plus an empirical anti-MRSA agent (**B**). *C-RP* C-reactive protein, C_{ss} steady-state meropenem concentration, *MIC* minimum inhibitory concentration, *MRSA* methicillin-resistant *Staphylococcus aureus*

5 Conclusion

Our PK/PD model predicted that in critically ill patients with documented Gram-negative HAP/VAP treated with CI meropenem monotherapy, attaining an aggressive C_{ss}/MIC ratio of 4–8 may grant very fast and intense C-RP decrease, thus anticipating efficacy. The next step towards the application of the developed PK/PD model for C-RP is its external validation in independent patient cohorts in order to evaluate the consistency of our predictions, in particular in different patient cohorts, antibiotic treatments and causative pathogens.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-024-01436-6.

Declarations

Ethics Approval and Consent to Participate The study was approved by the Local Ethics Committee (No. 308/2021/Oss/AOUBo on 24 May 2021).

Consent for Publication Due to the retrospective nature of this investigation, informed written consent was waived.

Availability of Data and Materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests The authors declare that they have no competing interests.

Funding This project has received funding from European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 861323.

Authors' Contributions CT analyzed and wrote the initial manuscript; PGC wrote the manuscript and interpreted patient data; MR collected patient data; TT collected and analyzed patient data; AS collected and analyzed patient data; CvH, PV and FP supervised the project.

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